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DEPARTMENT OF HEALTH AND HUMAN SERVICES

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CENTER FOR DRUG EVALUATION AND RESEARCH

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ARTHRITIS ADVISORY COMMITTEE

NDA # 21-042/S007, Vioxx (Rofecoxib, Merck)

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Thursday, February 8, 2001

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P R O C E E D I N G S

Call to Order and Introductions

MS. REEDY: Good morning and welcome to day two of the Arthritis Advisory Committee meeting. Again, thank you very much to our committee members for their generosity of time and sharing of their expertise in this important deliberation.

Drug safety is a cooperative effort involving manufacturers, public health providers and patients. Clearly, the goal is the optimizing through careful study to provide information that guides the right drug to the right patient at the right time. The study we will hear about today represents a significant effort and further characterization of a drug safety profile, in this instance rofecoxib. We look forward to today's deliberation and, again, thank you and welcome.

DR. HARRIS: The next item on the agenda is the presentation by Merck Research Laboratories. I want, as I did yesterday, to give Merck every opportunity to present their data. Since there will be discussions this afternoon, I am going to ask members of the committee to ask for questions of clarification but to save further discussion for this afternoon. Dr. Bonnie Goldmann?

Merck Research Laboratories Presentation

Introduction

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DR. GOLDMANN: Good morning. Mr. Chairman, members of the advisory committee, FDA, ladies and gentlemen, I am Dr. Bonnie Goldmann, from the Department of Regulatory Affairs, Merck Research Laboratories.

[Slide]

I would like to thank the advisory committee and FDA for the opportunity to present Merck's landmark Vioxx gastrointestinal outcomes research trial VIGOR, which definitively confirm, extend and generalize the gastrointestinal safety of rofecoxib, Merck's selective inhibitor of the cyclooxygenase enzyme COX-2. These results involve an array of hard clinical GI endpoints that confirm the GI safety results of our original NDA, now in a different disease population.

We believe these highly significant results merit modification of our product label to reflect a more appropriate presentation of the demonstrated GI safety that is specific to rofecoxib.

[Slide]

As you know, the cyclooxygenase family of enzymes are central to the metabolic conversion of arachidonic acid to a number of prostanoids. COX-1 is constitutively expressed in a number of tissues, and is responsible for maintenance of gastric glucosal integrity, normal platelet function and participates in several aspects of renal function, most notably regulation of salt and water regulation. COX-2 is the isoform induced at sites of inflammation and injury, and more recently has also been shown to have a constitutive role in renal salt and water balance.

Conventional non-selective NSAIDs, which during these presentations will be referred to simply as NSAIDs, inhibit both COX-1 and COX-2. As a result, they provide an anti-inflammatory and analgesic effect but, as a class, non-selective NSAIDs also affect renal handling of salt and water, impaired gastric mucosal integrity and inhibit normal platelet aggregation.

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NSAID gastropathy leads to serious upper GI side effects, one of the most common serious drug-related adverse events associated with non-selective NSAIDs. Based on extrapolations from the ARAMIS database, it has been estimated that NSAID gastropathy results in approximately 100,000 hospitalizations and 16,500 deaths per year.

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With this serious problem of non-selective NSAIDs in mind, we embarked on the development of selective COX-2 inhibitors based on the premise that selective inhibition would retain the anti-inflammatory and analgesic properties of NSAIDs. Renal salt and water effects would also be retained, at least in part, but COX-1-related functions in the gastric mucosa and platelets should be unaffected.

[Slide]

These predictions were crystallized in what has been called the COX-2 hypothesis. The hypothesis proposes that a selective COX-2 inhibitor should demonstrate anti-inflammatory and analgesic efficacy similar to non-selective NSAIDs, significantly improved GI safety compared to non-selective NSAIDs, effects on renal sodium handling similar to NSAIDs and no inhibitory effect on platelets.

[Slide]

The original NDA for rofecoxib, which was discussed with this committee in April, 1999, confirmed this hypothesis in patients with osteoarthritis and acute pain. Based on that data, FDA approved rofecoxib for the following indications: Vioxx is currently indicated for the relief of signs and systems of osteoarthritis, management of acute pain in adults, and treatment of primary dysmenorrhea. The recommended chronic dose for osteoarthritis is 12.5-25 mg per day, and for acute pain the short-term dose is 50 mg per day. Based on the previously published results from our Phase IIb rheumatoid arthritis efficacy study and the recently completed Phase III efficacy studies that have not yet been submitted to the FDA, we will be proposing 25 mg per day as a recommended dose for rheumatoid arthritis.

[Slide]

Rofecoxib is now available in 74 countries, and since its initial marketing in mid-1999 it is estimated that approximately 13 million patients have taken the drug in the U.S. and more than 24 million worldwide. Total exposure now exceeds 4 million patient years and, to this date, the general safety and tolerability profile of rofecoxib seen in postmarketing surveillance is consistent with the profile defined in the original NDA.

[Slide]

Today, we are here to discuss the VIGOR study. This single, large, multi-center, active comparator controlled trial of clinical outcomes in patients with rheumatoid arthritis was designed in consultation with regulatory agencies, including the FDA, to demonstrate the GI safety of rofecoxib based on clinically important GI events. In response to the agency's recommended, the dose of rofecoxib used in this study was twice the maximum recommended chronic dose for patients with osteoarthritis and rheumatoid arthritis. A subsequent speaker will discuss the rationale for dose selection in more detail.

[Slide]

As we shall describe today, and in conformance with the predictions of the COX-2 hypothesis, the results of VIGOR further established the clinical meaningful enhancement of GI safety for rofecoxib over non-selective NSAIDs, measured by significant clinical upper GI events with no effects on platelet function and minor effects on renal sodium excretion that are already reflected in the current product labeling for rofecoxib.

[Slide]

The agenda for today's Merck presentation is as follows: Dr. Nies will review the COX-2 selectivity of rofecoxib and the clinical data that set the stage for VIGOR. Dr. Reicin will then review the VIGOR results and put the study in the context of related clinical data, all of which broadly validate the COX-2 hypothesis.

The advisory committee members have previously received a background package from Merck that summarizes the large body of information in more detail than time allows us to discuss here this morning.

[Slide]

In addition to our speakers, Merck has brought several consultants to the meeting. These experts are available to facilitate the advisory committee's discussions and deliberations. Dr. Gerald Appel, Dr. Claire Bombardier, Dr. Christopher Hawkey, Dr. Marc Hochberg, Dr. Loren Laine, Dr. Marvin Konstam, Dr. John Oates, Dr. James Neaton, Dr. Walter Peterson and Dr. Scott Zeger.

I would now like to turn the podium over to Dr.

Nies.

COX-2 Selective and Previous Clinical Safety Data

DR. NIES: Good morning.

[Slide]

I am Dr. Alan Nies, in the Department of Clinical Sciences at Merck Research Laboratories.

[Slide]

I would like to review today some of the aspects of our development program to serve as a background for the VIGOR results that you will be hearing about.

[Slide]

We began the program with the hypothesis as outlined by Dr. Goldmann and that you heard about yesterday. We expected that a COX-2 selective inhibitor that did not have effects on COX-1, like rofecoxib, would demonstrate only a subset of the properties that were well-known with the NSAIDs. Thus, we expected that the efficacy would be equivalent to the NSAIDs but there would be differences in the safety profile and, in particular, there would be an improved safety profile in the gastrointestinal tract.

Today I will review the studies that showed the selective for COX-2 for rofecoxib, and I would like to talk about three special safety issues -- gastrointestinal safety which set the stage for the VIGOR trial, renal safety and cardiovascular safety. I will not be spending any time looking at the efficacy of the drug. This was well reviewed in the original NDA with this committee, jut to remind you that the doses that are approved for chronic use are 12.5 mg and 25 mg a day for osteoarthritis. As has been mentioned, our recently completed Phase III studies in rheumatoid arthritis indicate that 25 mg is the maximally effective dose in this disease as well.

[Slide]

Just one slide on the efficacy in osteoarthritis shown in this graph. This is a one-year study comparing rofecoxib to diclofenac. Patients come in, at this time are screened, and after they meet the screening criteria they are withdrawn from their NSAIDs and they flare. They are randomized at this point, here, and then they are continued on one of the three arms through the period of the trial.

As you can see, with pain on this axis, more pain is higher on the axis and all three treatments, 12.5 mg, 25 mg of rofecoxib and diclofenac 50 mg 3 times a say, are similar over the period of this year and the effect is maintained.

[Slide]

We defined selectivity in three major ways in this trial. First was assays using whole blood, and this assay I think is well familiar to many on this committee as a way to look at selectivity in patients or volunteers receiving the drug. Secondly, we looked at bleeding time and platelet function and, thirdly, we looked at the effect on cyclooxygenase activity in gastric mucosal biopsies of volunteers who were receiving the drug.

First with the whole blood assay, we did not find any effects of rofecoxib on COX-1 at any dose that we studied, and these doses were as high as 1000 mg single doses, and 375 mg multiple doses over a period of a couple of weeks, and with none of those regimens did we see any effect on COX-1. These doses, as you can appreciate, are much higher than the clinical doses of 12.5 and 25.

We did find, however, over the dose range that is used clinically that there was a dose-dependent inhibition of COX-2. This inhibition was similar to that seen with the NSAIDs. So, at a clinically effective dose of rofecoxib, one has inhibition of this whole blood assay of COX-2 at the 25 mg dose, for instance, at about 60-80 percent inhibition and that is the same degree of inhibition one sees with drugs such as diclofenac and ibuprofen used at their high clinical doses.

[Slide]

The dose-dependent effects of rofecoxib are consistent with its linear pharmacokinetics. This just shows the area under the curve, shown on this side, versus dose. You can see the linearity. Area under the curve is a way to look at exposure of the drug. It is the curve on concentration versus time. You can see that this goes up linearly with dose. This is independent of food and is consistent across age groups, and such consistency and linearity is not seen with all drugs, as you are probably aware.

[Slide]

Secondly, we looked at the effects on bleeding time and platelet function as a way to look at COX selectivity. Rofecoxib does not affect bleeding time or platelet aggregation. For the bleeding time we studied doses up to 375 mg, multiple doses. Here, shown on the left, is placebo, 250, 375. I think it is evident that there is no effect of the drug on bleeding time.

We studied platelet aggregation at the dose of 50 mg and we did not see any effect of rofecoxib on inhibiting platelet aggregation. Inhibition is shown as an increase on this axis.

You can see the effects of aspirin. Aspirin at 81 mg, which is the so-called low dose aspirin for cardioprotective reasons, inhibits platelet aggregation 90 percent or so, and that is shown on this slide. It is really the gold standard for what one needs to achieve to get platelet function inhibited for cardiac protection.

[Slide]

The last thing that we looked at for selectivity was the assays of cyclooxygenase in gastric mucosal biopsies. We originally showed to this committee, back in '99, some data that was developed for 25 mg of rofecoxib and that was included in our NDA. Today I will show you data with a higher dose, 50 mg.

[Slide]

The way the study was done, the individuals took the drugs for 5 days, and then 4 hours after their last dose they were endoscoped and had gastric mucosal biopsies. The ability of that biopsy tissue to generate prostaglandins was used as an index of the synthetic capacity in the COX activity. Since the gastric mucosa normally only contains COX-1, this is really another way of looking at COX-1.

On the left are shown the effects naproxen 500 mg twice a day. We see the expected effect of naproxen to reduce the ability of the mucosa to produce prostaglandins. On the right is shown rofecoxib 50 mg a day. This is the high dose that we used in VIGOR, twice our maximum dose on the market, and it did not have an effect. This is similar to the results that we had seen at 25 mg.

[Slide]

I would now like to turn to selective aspects of the safety. First I will review some of the GI special studies that were done and were submitted in our NDA as this sets the groundwork for VIGOR. I will then go through some renal and cardiovascular issues.

[Slide]

We did two sets of endoscopic studies during the NDA development. The first was a study in normal subjects. This was done early in the program, really before we had an idea of what our dose would be. So, we chose a dose of 250 mg of rofecoxib and gave this for a week to normal volunteers. They were endoscoped at the beginning and the end of that week. This was compared with a dose of aspiring of 650 mg 4 times a day and ibuprofen 800 mg 3 times a day in separate groups. At the end of the week we found that the 250 mg of the rofecoxib, which is really an order of magnitude higher than our clinical dose, was far superior to the aspirin and the ibuprofen. There was also a placebo group in this and the results were close to placebo with our drug.

We then did some studies with osteoarthritis patients. We did to replicative studies there. We looked at 25 mg and 50 mg of the rofecoxib and we compared it in this study to ibuprofen 800 mg 3 times a day. This went on for 6 months. We also had a placebo group for 4 months. The endoscopies were done at baseline, at 6 weeks, at 12 weeks and then at 6 months.

[Slide]

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The data from these studies that we have shown to this committee previously, and these data are in our label, are shown here. These are the two studies. There was a U.S. study and a multinational study. The 12 week and 24 week endoscopies are shown on each side, and this is the cumulative incidence rate of gastroduodenal ulcers. The placebo is only in the 12 week because it was discontinued after that time point.

I think it is clear that ibuprofen, shown here, in these two studies, causes a large number of ulcers over this period of time and that rofecoxib at both doses is markedly superior to ibuprofen in both studies, and at the 12-week time point you can see how it compares to placebo.

[Slide]

The last of the special GI safety studies that we did was to look at the entire GI tract. This was done in sort of an indirect way. First we looked at fecal blood cell loss. We injected radio labeled red cells and looked at the excretion in the feces. We also looked at the absorption of normally non-absorbable EDTA as an index of how the drugs altered intestinal permeability. The comparators in these trials included ibuprofen at the doses I talked about before, 800 3 times a day, and indomethacin, 50 mg 3 times a day.

In both of these trials the 25 mg and 50 mg dose of rofecoxib was superior to NSAIDs, and in both of these trials they were also statistically equivalent to placebo.

[Slide]

I would now like to move on to the renal aspects of COX-2 inhibition.

[Slide]

It is well-known that prostaglandins have effects in the kidney. Box COX-1 and COX-2 are present in the normal kidney. This wasn't apparent early on when we started but it became apparent fairly early, that COX-2 is present in mammalian kidney. We do know that prostaglandins are involved in renal physiology. They are involved in control of glomerular filtration rate, in control of renin secretion, and they have effects on sodium, potassium and water homeostasis. It is well-known that NSAIDs produce a small incidence of edema and hypertension.

[Slide]

Throughout our development program, it has become clear that the COX-2 selective inhibitors are equivalent to the non-selective NSAIDs in many of their renal effects and particularly in reducing the urinary sodium excretion. This does appear to be dose related. For instance, the 12.5 mg of rofecoxib appears to have less of this effect than 25 and 50 mg.

[Slide]

Shown in this slide are some data from a recently completed study looking at an NSAID, naproxen 500 mg twice a day, rofecoxib 25 mg a day, celecoxib 200 mg twice a day. These are the highest approved doses for the COX-2 inhibitors and a medium dose for naproxen but a usually used dose of naproxen.

On this axis, the Y axis, is the change from baseline in daily urinary sodium excretion. This is a study that was done in 60-80 year old patients who were brought into sodium balance on a metabolic ward. They were on a normal to high sodium diet, 200 mEq of sodium per day. At baseline they were started on one of these four regimens. As you can see, the effects occurred over this period of time, and almost all of the action occurs within the first two or three days where there is an inhibition of sodium excretion or sodium retention occurring, which then comes back into balance after three days and is maintained over the 14-day period.

The statistical hypothesis was that rofecoxib and celecoxib would be similar, and we had defined similarity bounds for that and the study showed, indeed, that the drugs were similar. In fact, they were similar to naproxen, and all of these were different than the placebo.

[Slide]

I would next like to turn to the cardiovascular issues. I know that that is of great interest and importance to the committee and to us, particularly as it relates to the platelet-endothelium interactions.

[Slide]

I would like to just review briefly a little bit about the biochemistry. Some of this was reviewed yesterday as well. Platelets contain only COX-1 and this produces thromboxane A-2. Thromboxane A-2 promotes platelet aggregation, and that is important for normal hemostasis. But, it can also be a pathological problem. For instance, in the setting of atherosclerosis with a ruptured plaque, platelets aggregate and can occlude the vessel, producing an occluding thrombus.

Non-selective NSAIDs and aspirin can inhibit COX-1. If they do this sufficiently or enough, this can produce a change in platelet aggregation. Now, this can be protective against the thrombus production that is pathologic but it also interferes with normal hemostasis. So, in the studies that are done with anti-platelet drugs frequently there is some excess bleeding and often it is seen in minor bleeding episodes such as epistaxis and ecchymosis.

In order to have a sufficient effect on thromboxane to really have an effect on platelet aggregation, one has to inhibit thromboxane production by greater than 90 percent. Aspirin certainly does this because of its mechanism-based irreversible inhibition of COX-1. Some of the NSAIDs also have this potential.

[Slide]

I would like to show you some data that were generated during our NDA process, submitted in the NDA, on various NSAIDs that we used in our program, both in the VIGOR program and in our Phase IIb/III program on platelet aggregation.

On this axis is the amount of inhibition of platelet aggregation, and various drugs are listed along here. You can see that placebo and rofecoxib has no effect on platelet aggregation. Aspirin, as the gold standard, has this 90 percent or more inhibition. Then, the other NSAIDs are arrayed along here, naproxen, ibuprofen and diclofenac.

I would like to focus on these two, ibuprofen and naproxen, which look as if they may provide a substantial degree of platelet inhibition.

[Slide]

To do that over a time course, this is what we see. This study looks over a dosing interval with naproxen, ibuprofen and placebo. This is at steady state so the zero time point is the end of the previous dosing interval. So, for naproxen that is 12 hours after a dose; for ibuprofen it is 8 hours after a dose. Then we measured it for the next 8 hours. Naproxen, as you can see, maintains over this period of time a 90 percent inhibition of platelet aggregation, whereas ibuprofen, because of its short half-life presumably, does not have a sustained effect and in order to have complete cardioprotection from this mechanism one has to sustain that effect over the full time that patients are taking the drug. Ibuprofen, at least as given in this regimen of 800 mg 3 times a day, does not do that, whereas naproxen 500 mg twice a day does do that.

[Slide]

Just to compare naproxen and aspirin effects in kind of a numeric say here to give you an impression of how close they are, the mean inhibition from baseline with aspirin is 92; 93 with naproxen. The medians are the same and the range is the same. So, I think from the mechanistic point of view one can see that naproxen does have the potential for producing effects that are like aspirin.

[Slide]

So, this raises the question can some NSAIDs, such as naproxen, have aspirin-like cardioprotective properties by potently inhibiting platelet aggregation? In thinking about this question over the past few months, we have developed both some animal data and some epidemiologic data that supports this, and this will be mentioned again by Dr. Reicin in the next talk.

[Slide]

Returning to the platelet-endothelium interface, on the other side of the issue we have the endothelium. Tne endothelial cell is really a lot harder to study than the platelet. It is not easy to isolate and it is a much more complicated cell than the platelet. The endothelium, in terms of the prostanoid that it produces it is largely prostacyclin. This inhibits platelet aggregation, and is thought to be important for the balance between these two.

The cyclooxygenase responsible for prostacyclin product has classically been thought to be COX-1, as was mentioned yesterday. If you take out vascular tissue and look at endothelial cells, look at immunohistochemistry, you really only find COX-1. So, it was really a surprise when, during our development program, even in what were normal volunteers it was found that the drugs rofecoxib and celecoxib reduced the urinary excretion of a metabolite of prostacyclin.

Although we don't know the cells that produce the prostacyclin that result in this metabolite coming out in the urine, this implied that these drugs had an effect on synthesis of prostacyclin and the implication is that the endothelial cell is part of that and, so, COX-2 must be involved in the endothelial cell. This means then that the non-selective NSAIDs, as well as the COX-2 inhibitors, have the potential for reducing prostacyclin production.

[Slide]

This show the two studies that I was referring to. These were both done at the University of Pennsylvania but they were two separate studies. On the left is a study with celecoxib single dose treatment 400 mg versus ibuprofen. This is data 6 hours after dose. Urinary excretion of the metabolite of prostacyclin -- this metabolite, urinary 2,3 dinor-6-keto-PGF-1alpha, is usually in the literature called PGIM, and you can see the effect of placebo here and then the effects of the two drugs on the excretion, which is on this axis. With rofecoxib 2 weeks of therapy at 50 mg a day, a similar effect.

[Slide]

These effects indicate that the COX-2 selective inhibitors reduce by about 60 percent potentially the reduction in systemic prostacyclin synthesis. We don't know what the importance of a 60 percent reduction is on this side of the issue. We do know it takes 90 percent inhibition on this side in order to see an effect. I think the data are even more hard to interpret because the endothelial cell also produces other potent anti-platelet factors. The best known of these and the most well studied, at least recently, is nitric oxide, and this is produced independent of the cyclooxygenase system. So, this redundancy in the system I think makes interpretation of the 60 percent reduction of one part of it hard. Nonetheless, I think this raises the issue as to what is the clinical importance of inhibiting system prostacyclin synthesis without inhibiting platelet aggregation.

[Slide]

Because of these two questions, we were sufficiently concerned that there might be an alteration in the balance that first we examined our Phase IIb/III database carefully to see whether there was any evidence of excess cardiovascular events. Just to remind you that the comparators there were ibuprofen 800 mg three times a day, diclofenac 50 mg three times a day -- those two drugs probably do not maintain sustained suppression of platelet aggregation. We did not see any signal in our Phase IIb/III database. But we decided that the most rigorous way that we could look at this was to establish a standard operating procedure to capture and adjudicate all cardiovascular events in all future COX-2 inhibitor trials, not just with rofecoxib but with subsequent entries to the market that we would be studying, and that was set up in 1988. This was prior to VIGOR and actually we set that up prior even to putting in the initial NDA.

[Slide]

Just to conclude this introductory talk, rofecoxib is a COX-2 inhibitor without effects on COX-1 at and above the clinical doses.

Rofecoxib 12.5 mg and 25 mg once daily is equally effective to NSAIDs in osteoarthritis and, as I have mentioned, 25 mg is the maximally effective dose in rheumatoid arthritis, as we have recently seen in our Phase III data but these have not yet been reviewed by the agency. Rofecoxib's effects on the gastrointestinal mucosa are significantly less than the NSAIDs. The renal effects of the COX-2 inhibitors are similar to the NSAIDs.

Platelet thromboxane production is variably reduced by the NSAIDs; not all of them produce effects that would be important here but some do. But the COX-2 inhibitors have no effect on this and that I think is very important. And, systemic prostacyclin synthesis is reduced by both.

This really summarizes the COX-2 hypothesis then that the clinical effects that we have seen are really a consequence of its selective inhibition of COX-2 and its lack of effect on COX-1, and this supports the initial hypothesis.

I would now like to introduce Dr. Alise Reicin, who will discuss with you the details and the findings of the VIGOR trial.

VIGOR Study and Related Clinical Data

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Date: 3/9/01 Time: 2:01:08 PM

DR. REICIN: Dr. Nies has just presented to you the background behind the COX-2 hypothesis, and I will be discussing with you today the clinical profile of rofecoxib which was developed on the basis of that hypothesis.

[Slide]

I am going to begin my discussion with a review of studies and analyses that were done to determine if rofecoxib was associated with a clinically important reduction in clinically important GI outcomes. The focus of that discussion will be the results of the recently completed large GI outcomes study done in patients with rheumatoid arthritis, and I will refer to this study as the VIGOR study.

I will also be reviewing with you the results of our prespecified analysis on clinical upper GI events with our Phase IIb/III OA studies. The results of this analysis were previously presented to this committee in 1999.

I will then have a brief review of efficacy measurements in the VIGOR study, followed by a review of general safety and cardiovascular safety. Again, for these latter two topics the focus will be VIGOR but in the context of the overall development program.

[Slide]

As Dr. Nies discussed, as a part of the Phase III Vioxx development program, a series of studies were performed which evaluated the effect of rofecoxib compared to non-selective NSAIDs as markers of NSAID-induced GI toxicity. These studies, which included surveillance endoscopy studies and studies which evaluated subclinical GI blood loss, clearly demonstrated the improved GI safety profile of rofecoxib but it was important to determine whether the results of those studies could be translated into a reduction in clinically important GI outcomes, the type of outcomes that are important to patients and to physicians who are caring for those patients.

I think, as you will see today, we have in fact demonstrated that these endoscopy studies were predictive. We have now demonstrated a significant reduction in clinically important upper GI events in rofecoxib compared to non-selective NSAIDs in patients with RA in the VIGOR study and also in patients with osteoarthritis in our combined Phase IIb/III OA analysis.

[Slide]

The primary and secondary endpoints for the study were defined in collaboration with the FDA. The primary endpoints were what I will refer to as clinical upper GI events. In the past they have been known as PUBs, and these include gastroduodenal perforations, symptomatic gastroduodenal ulcers, ulcers which are rarely complicated by gastric outlet obstruction, and upper GI bleeding.

When I am talking about symptomatic ulcers, we are specifically referring to ulcers that were picked up because patients presented with signs or symptoms for which an investigator initiated a workup. We were very careful during our studies not to have an algorithm for investigators to use but, instead, to encourage them to make decisions about whether to initiate a workup based on the decisions they would make in their medical practice.

A subgroup of these events I will refer to as complicated upper GI events. These are more severe. These are the type of events for which patients often present to in an emergency room for urgent evaluation. They include gastroduodenal perforations, obstructions, and a subgroup of the upper GI bleeds which I will refer to as major upper GI bleeds. These are bleeds that are associated with the need for a blood transfusion, evidence of volume depletion or a two gram or more drop in hemoglobin.

[Slide]

In both the Phase IIb/III OA analysis as well as in the RA outcome study a process was established for the review and adjudication of clinically important GI events by an outside panel of experts. Their process started with the blinded investigators who evaluated and then reported suspected clinical events. Endpoint packages were then put together which included source documents, as well as a narrative, and these were went to an independent blinded adjudication panel who reviewed the source documents and, based on prespecified stringent case definitions, classified the events as confirmed or unconfirmed and complicated or uncomplicated.

[Slide]

We will now switch to the VIGOR study. VIGOR was a multinational study. It was conducted in 301 clinical centers in 22 countries and on five continents. There were three major external committees which oversaw the conduct of the study. The first was the blinded endpoint adjudication committee, and I have already reviewed with you the function of that committee. In addition, there was a blinded steering committee, in essence an oversight committee. This committee was charged with the overall scientific and operational direction for the study. They reviewed and approved the original protocol as well as all protocol amendments. Lastly, there was an independent data safety and monitoring board who reviewed interim safety analyses and, based on the results of those analyses, could request modifications in the protocol or early termination of the study to ensure patient safety. However, no such requests were made during the conduct of the study.

[Slide]

There were several prespecified objectives for the

VIGOR study. The primary objective was to demonstrate that rofecoxib at twice the maximum chronic dose would be associated with a significant reduction in confirmed clinical upper GI events. So, our primary endpoints were events, clinical upper GI events that were confirmed by the adjudication committee. In addition, there were several secondary objectives and they were to demonstrate a significant reduction, in rofecoxib compared to naproxen, of confirmed complicated upper GI events, confirmed plus unconfirmed clinical upper GI events and confirmed plus unconfirmed complicated upper GI events.

Most of the literature on NSAID-related GI bleeding relates to GI bleeds from the upper GI tract. However, there are some epidemiologic studies which suggest that patients who take non-selective NSAIDs are also at an increased risk from lower GI bleeding and, therefore, we also had an exploratory objective to demonstrate a reduction in all episodes of clinical GI bleeding. This means GI bleeding from either the lower or the upper GI tract. I am not here talking about asymptomatic drops in hemoglobin. We are talking about clinical GI bleeds that were reported by investigators.

[Slide]

Why did we choose to study patients with rheumatoid arthritis instead of patients with

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osteoarthritis, or potentially a combination of the two? Well, as has been shown to this panel previously and I will again show you today, the improved GI safety with rofecoxib was previously demonstrated in patients with OA in our combined upper GI event analysis. Therefore, the steering committee raised potential ethical concerns about essentially repeating the same experiment in the same patient population.

On the other hand, patients with rheumatoid arthritis are routinely treated with chronic NSAIDs, and this is a patient population that is known to be at high risk for NSAID-related events. Lastly, the use of RA patients would allow us to both confirm the results of the Phase IIb/III GI safety analysis, as well as to extend those results to a completely different patient population and, therefore, would extend the generalizability of the results.

[Slide]

In our Phase IIb/III OA studies the main NSAID comparators were diclofenac and ibuprofen. Naproxen was chosen for this study because, first of all, in the U.S. and many other countries it is the most commonly prescribed NSAID for the treatment of rheumatoid arthritis and, in addition, it would give us yet another NSAID against which rofecoxib had been compared. And, 500 b.i.d. was chosen as the dose because it is the most commonly used dose for the treatment of rheumatoid arthritis.

On the other hand, as requested by the FDA, due to the important issue of dosage creep in clinical practice, rofecoxib was studied at two times the maximum chronic dose, 50 mg. So, 50 mg is two to four times the dose for osteoarthritis, and the FDA has questioned in their background package whether 50 mg would, in fact, be the dose for the treatment of rheumatoid arthritis. However, the results of our recently completed Phase IIb and III studies, which have not yet been reviewed by the agency, confirm that 25 mg is the dose for the treatment of rheumatoid arthritis. These studies demonstrated that 50 mg did not provide additional efficacy compared to 25 mg, and both 25 and 50 provided efficacy which was similar to naproxen at 1000 mg daily. Therefore, by studying the most commonly used dose of naproxen compared to two times the maximum dose of rofecoxib would provide rigorous testing of the GI safety of rofecoxib.

[Slide]

In VIGOR, over 8000 patients were randomly assigned to either rofecoxib 50 mg once a day or naproxen 500 b.i.d. in a double-blind manner. Randomization was stratified by a prior history of a clinical upper GI event. There was a brief washout of prior NSAID therapy, minimum three days, which was essentially to ensure pharmacologic separation of prior NSAID therapy with study therapy. This was not done to elicit a flare in patients' rheumatoid arthritis as you do in an efficacy study.

During the study patients were seen after randomization at six weeks, four months, every four months thereafter and then at study termination, and they were contacted in between clinical visits with frequent telephone calls.

[Slide]

The duration of the study was determined both by time and the cumulative number of endpoints, and the study was terminated based on prespecified stopping guidelines which were in the protocol. A minimum of all three of the following need to have occurred for the study to be terminated: 120 confirmed clinical upper GI events had to have occurred; plus, 40 confirmed complicated events; and, a minimum of six months had to have elapsed since the last patient was randomized. All of these criteria were, in fact, met prior to termination of the study. The study was terminated approximately 13 months after the first patient was randomized and 8.5 months after the last patient was randomized.

[Slide]

In order to be enrolled in the study, patients had to have a diagnosis of rheumatoid arthritis. They had to be

50 years of age or older, or 40 years of age or older if they were on chronic systemic corticosteroids, and they had to have been felt by their investigator to require NSAIDs for at least one year. All patients were tested for occult blood screening and a positive test resulted in exclusion from the study. In addition, patients were excluded who were using medications that might have confounded the GI safety results of the study. Therefore, patients who were using aspirin, anticoagulants, anti-platelet agents or anti-ulcer medications, such as proton pump inhibitors or misoprostol were excluded. However, over-the-counter doses of H-2-receptor antagonists were allowed prior to entry and during the study.

Before I move on, I do want to point out that we did appreciate the importance of the question of whether a safety advantage would be maintained in patients who were taking aspirin concomitantly with rofecoxib. However, we also knew, as Dr. Goldkind pointed out during yesterday's discussion, that we would not be powered to answer that question if only 10-20 percent of the patients enrolled in the study were concomitant users of aspirin. Because, as I will show you today, endoscopy studies are predictive of GI outcomes for rofecoxib, we have designed and have ongoing an endoscopy study which is specifically designed to evaluate this.

[Slide]

The mean age of patients in the study was 58, though patients as old as 88 and 89 were also randomized. In keeping with the patient's diagnosis of RA, 80 percent of them were female; 8 percent had a prior history of an upper GI event; and about 2.5 percent had a prior history of complicated upper GI event. Systemic corticosteroids were used by a little over 50 percent of patients and a little over 40 percent of patients were *H. pylori* positive at baseline. The mean duration of the patients' rheumatoid arthritis was approximately 11 years, and about 97 percent of patients met four or more ACR criteria for the diagnosis of RA. So we know that, in fact, we did this study in a rheumatoid arthritis patient population. Methotrexate of other DMARDs were used in over 80 percent of patients in the study.

[Slide]

Over 9500 patients were screened. Over 8000 patients were randomized, and over 71 percent of patients completed the study, meaning that they remained on study drug at the time of the study termination. This completion rate was quite high and, in fact, when the study was designed it was assumed that there would be a 50 percent dropout rate based on the previous literature.

Of the 29 percent of the patients who prematurely discontinued from the study, the reasons for discontinuation were similar between the two treatment groups and 16 percent of patients discontinued for an adverse experience in both groups, and this does include clinical upper GI events. You can see low and similar rates of discontinuation for lack of efficacy.

[Slide]

The median time that patients were on treatment was 9 months, but you can see up to a maximum of 13 months for those patients who were enrolled at the beginning of the enrollment period. There was almost 1700 patient years on treatment in both groups, and all patients and all events were included in all analyses for their entire duration of time on treatment, plus an additional 14 days, to ensure that we captured all endpoints potentially related to study therapy. This is consistent with the intent-to-treat approach and it means that despite the relatively short three-day washout period there was no censoring of early events which may have been related to prior NSAID use.

[Slide]

During the study, 190 patients had clinical upper GI events reported by their investigators. Of those 190 patients, 170 [sic] patients had confirmed clinical upper GI events. These are events that were confirmed by the adjudication committee. Fifty-three of these patients, of the 177 [sic], had confirmed complicated upper GI events. As you can see, there were 13 patients with unconfirmed clinical upper GI events. The majority of these were patients who had upper GI bleeds and did not have enough source documentation to meet prespecified stringent case definitions. During most of my discussion today I will be concentrating on the confirmed events, however, the results of confirmed plus unconfirmed events were similar because of these 13 patients 11 were on naproxen.

[Slide]

The results of our primary endpoint are presented on this slide. The vertical axis shows the cumulative incidence of confirmed clinical upper GI events. Time is on the horizontal axis. I think you can see there is early separation of the curves. That separation is maintained over time. The relative risk of sustaining a confirmed clinical upper GI event on rofecoxib compared to naproxen was 0.46, which corresponds to a 54 percent reduction, and that was highly statistically significant in favor of rofecoxib, with a p value of less than 0.001.

[Slide]

The results of the key secondary endpoint, confirmed complicated upper GI events, are presented here. I think you can see that the curves look quite similar to what I just showed you for the primary endpoint. The relative risk of sustaining a confirmed complicated upper GI event on rofecoxib to naproxen was 0.43. That corresponds to a 57 percent reduction, again statistically significant in favor of rofecoxib.

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Another way to look at the data is to compare across the treatment groups the rates per 100 patient years for these clinical upper GI events. I am showing here three of the prespecified endpoints. I have already shown you the results for confirmed clinical upper GI events and confirmed complicated upper GI events. The relative risk is shown above with the 95 percent confidence intervals and, again, both of those were significant.

In addition, over here, on the right, are all episodes of clinical upper GI bleeding. So, these are GI bleeds from the upper and the lower GI tract. You can see here also that the relative risk of sustaining a clinical upper GI bleed on rofecoxib compared to naproxen was 0.38. That corresponds to a 62 percent reduction and, again, this was significant.

[Slide]

To determine if rofecoxib was associated with reduced incidence of GI bleeding from both the upper and lower GI tract, we did some exploratory analyses and broke this down into upper GI bleeds, major upper GI bleeds and lower GI bleeds. Again, you can see significant reductions in all of these endpoints. The relative risk of sustaining an upper GI bleed on rofecoxib was 0.36, corresponding to a 64 percent reduction. The relative risk of sustaining a major upper GI bleed was 0.37, corresponding to a 63 percent reduction, and the relative risk of sustaining a lower GI bleed on rofecoxib compared to naproxen was 0.46, corresponding to a 54 percent reduction and, again, all were significant.

[Slide]

The nature of the events that made up the primary endpoint are delineated on this slide. As predicted from the epidemiology, the most common events on naproxen were gastric ulcers, followed by duodenal ulcers and upper GI bleeds and all of these were reduced in the rofecoxib group compared to the naproxen group.

[Slide]

There were consistent significant reductions in relative risk on rofecoxib compared to naproxen in all of our endpoints, as demonstrated on this slide. The orange diamonds here point to the relative risk of sustaining a GI endpoint on rofecoxib compared to naproxen. The white lines show the 95 percent confidence intervals. The diamonds that fall to the left of 1 favor rofecoxib. The top five rows are five prespecified endpoints; the bottom three were the three exploratory endpoints and, again, you can see very similar relative risks. Risk reductions ranged from 54 to 64 percent.

[Slide]

Several risk factors for clinical upper GI events are known from the literature. These include age greater than 65; the use of systemic corticosteroids; a prior history of a GI event; and evidence of *H. pylori* infection. The point estimates indicate that there was a numerically reduced risk of sustaining a confirmed upper GI event on rofecoxib in both patients with and without each of these risk factors. The study was not designed nor powered to achieve significant reductions in each subgroup and yet, surprisingly, we did demonstrate significance in virtually all of the subgroups tested.

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We also evaluated low risk patients, and I will put low risk in quotes here. What I am referring to are patients who are younger than the age of 65. They are not *H. pylori* positive. They weren't using systemic corticosteroids and they didn't have a prior history of a GI event and you can compare those to patients who had one or more risk factors.

As expected, the overall incidence of events in this "low risk" group was lower than those who had one or more of these events. As you can see, the rofecoxib group in particular had a very low incidence, 0.2 percent. But, importantly, the GI safety advantage of rofecoxib was maintained both in patients with and without any of these risk factors. There were significant reductions in both of these groups, ranging from 51-88 percent.

[Slide]

I am now going to briefly review for you the results of our Phase IIb/III prespecified clinical GI events analysis that was done in patients with osteoarthritis. I would like to compare those to the results of the VIGOR study. This prespecified analysis included all of our Phase IIb/III studies done in patients with osteoarthritis. Over 3000 patients were randomized to rofecoxib in doses which ranged from 12.5 to 50 mg, with a mean dose of 24.7 mg.

We had a combined NSAID comparator group that was prespecified and included diclofenac, ibuprofen or nabumetone in over 1500 patients, but really the majority of the exposure here was to diclofenac and ibuprofen. There was also a small placebo group of over 500 patients who were on therapy for up to four months.

The primary prespecified endpoint was confirmed clinical upper GI events, the same primary endpoint that we had from VIGOR. The secondary endpoint was confirmed and unconfirmed clinical upper GI events. As I noted earlier, the same adjudication committee from VIGOR was used and the same process for the adjudication of these upper GI events.

There were 55 upper GI events reported in our Phase IIb/III studies. Of these, 49 were confirmed upper GI events and there were six unconfirmed events. Similar to what we saw in VIGOR, all six of these events were unconfirmed GI bleeds and, in fact, all six were on one of the NSAIDs.

[Slide]

Similar to what I showed you for VIGOR, these are the results of the primary endpoint. This is time to confirmed clinical upper GI events. The relative risk for sustaining a confirmed upper GI event on rofecoxib compared to the combined NSAID comparators was 0.45; 55 percent reduction, statistically significant in favor of rofecoxib.

I am not going to show you the results of the secondary endpoint of confirmed plus unconfirmed events, but when you add in those six events that were on the NSAID comparators the relative risk is 0.35, corresponding to a 65 percent reduction and, again, significant in favor of rofecoxib.

[Slide]

Although we have limited data on placebo, comparisons are of interest and since placebo patients were only treated for a maximum of four months, we performed a four-month analysis. The rate per 100 patient years of confirmed clinical upper GI events -- I think you can see the number of events overall is quite small, but the rates are similar on placebo and rofecoxib and less than the combined NSAID group.

[Slide]

Lastly, this represents a side-by-side comparison of the rates of confirmed clinical upper GI events per 100 patient years from the OA Phase IIb/III studies, on the left, and from the VIGOR study in patients with rheumatoid arthritis, on the right. The relative risk reductions are above them. What you can see is that the relative risk in the OA studies is 0.45 compared to 0.46 in the rheumatoid arthritis studies. Therefore, despite the fact that the patient populations were different -- one was in OA and one was in RA -- despite the fact that the NSAID comparators were different -- one was a single study, one was multiple studies and this one had multiple doses and the VIGOR study was at the 50 mg dose -- the results were highly and surprisingly consistent.

[Slide]

Before I conclude the GI safety section of the talk, I want to take a moment to review a prespecified analysis done to examine the overall GI tolerability of rofecoxib. As you know, NSAIDs are commonly associated with

GI symptoms. The etiology of these symptoms really is unknown and the correlation with mucosal injury is quite poor. However, these symptoms are important because they often result in the need to discontinue treatment with non-selective NSAIDs. In fact, in VIGOR the five most common reasons for discontinuing from the study, aside from gastric ulcers, were GI symptoms, such as dyspepsia and epigastric discomfort.

As illustrated in this slide, in both the Phase IIb/III OA studies, over on the left, and in VIGOR there was a significant reduction in discontinuations due to GI and abdominal adverse experiences on rofecoxib compared to the NSAID group.

[Slide]

In summary, rofecoxib significantly decreased the risk of clinically important GI events, in both our Phase IIb/III OA analysis and in VIGOR, by 54-65 percent. We have demonstrated consistent and significant effects in all prespecified endpoints and consistent effects in both high and low risk subgroups. The improved GI safety has been demonstrated independently in both OA and RA, and we believe that these data warrant modification to the current rofecoxib label to distinguish the GI safety profile of rofecoxib compared to non-selective NSAIDs.

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VIGOR was designed specifically to test the GI safety of rofecoxib and not to demonstrate its efficacy in patients with rheumatoid arthritis. However, to ensure that the GI safety comparison in VIGOR was not done at a dose of rofecoxib which was sub-therapeutic compared to naproxen, four efficacy measurements were included in the study.

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The study employed a non-flare design to monitor symptomatic stability rather than improvements from baseline, and the efficacy objective was to assess RA disease activity during treatment with rofecoxib versus naproxen using standard efficacy measurements, which included a patient global assessment of disease activity, an investigator global assessment of disease activity, the percent of patients who discontinued due to lack of efficacy and then, at the request of the FDA, we also included the modified health assessment questionnaire, which is in essence a disability questionnaire.

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Efficacy was virtually identical in both treatment groups in all endpoints measured. The top three rows show you the changes from baseline in the three questionnaires. Negative values are consistent with improvements. Despite the fact that we didn't have a flare, there were small and similar improvements in both treatment groups, and discontinuations due to lack of efficacy occurred at a low incidence and a similar rate in the two treatment groups.

[Slide]

Therefore, in VIGOR rofecoxib and naproxen demonstrated similar efficacy in the treatment of RA, and this is consistent with our Phase IIb/III data which demonstrated that both 25 and 50 mg of rofecoxib had efficacy which was similar to 1000 mg a day and, again, the agency has not yet reviewed those studies.

[Slide]

I am now going to turn to a review of rofecoxib's general safety. As I discuss this, I think it is important to remember that the study was designed specifically as a GI safety study and not a general safety study and, therefore, the dose of rofecoxib studied was two times the maximum chronic dose.

[Slide]

However, at that dose the safety profile of rofecoxib demonstrated similar efficacy to what we saw in our Phase IIb/III program and, therefore, is consistent with current labeling. In the Phase IIb/III studies rofecoxib was generally well tolerated, as I showed you already; demonstrated a superior GI tolerability compared with non-selective NSAIDs.

In addition, as you would expect, based on the effects of COX-2 inhibition on renal sodium handling, the incidence of renal vascular adverse experiences, such as edema and hypertension, were similar to NSAIDs within the clinical dose range at 12.5 and 25 mg. At 50 mg, which is two times the maximum dose, there is an increase in these adverse experiences. This increase is reflected in our current labeling and is not unexpected since these adverse experiences are dose-related for NSAIDs and, as you increase the dose from 25 to 50 mg, you do get a doubling in systemic exposure since rofecoxib has dose proportional kinetics within this dose range. Lastly, rofecoxib, like other NSAIDs, is associated with a low incidence of increased transaminases. It occurs in about 0.5 to 1 percent of patients. The incidence of these increases in the Phase III studies was similar to ibuprofen and significantly less than diclofenac.

[Slide]

The next two slides are going to give you a high level overview of clinical and laboratory adverse experiences reported in VIGOR. This will be followed by a series of slides which explore in greater detail specific safety issues of interest. Statistical testing was done only on adverse experience analyses which were prespecified and, therefore, throughout general safety discussions p values will only be shown for predefined safety analyses.

In VIGOR the overall incidence of clinical AEs, drug-related AEs and discontinuations due to AEs were similar in the two treatment groups. There was a small difference, which was statistically significant, in serious adverse experiences with rofecoxib having slightly more than naproxen. This did not carry over to serious drug-related adverse experiences which were, in fact, high on naproxen compared to rofecoxib. I will be discussing these during the cardiovascular part of my talk.

[Slide]

Overall, the incidence of laboratory adverse experiences was low, occurring in approximately 10 percent of patients. Serious AEs and discontinuations for lab AEs, again, were low and with similar rates in the two treatment groups.

[Slide]

Prespecified adverse experiences were chosen based on the known safety profile of NSAIDs and COX-2 inhibitors, and these AEs included AEs related to GI tolerability, renal sodium handling, renal function and hepatic function. Discontinuations due to these adverse experiences were generally prespecified as the primary approach to analyze the clinical importance of these adverse experiences. This slide summarizes the results of these analyses.

Statistical testing was done on all of these adverse experiences and significant reductions were seen for only two of them, discontinuations due to digestive system AEs, which I have shown you, which was in favor of rofecoxib, and discontinuations due to hypertension related AEs, which was in favor of naproxen. Discontinuations due to edema related AEs, all AEs of congestive heart failure, discontinuations due to renal related AEs and discontinuations due to hepatic AEs were not significantly different between the two treatment groups.

[Slide]

In this slide and in the next several slides the crud incidence of specific AEs is shown in the hatched bars and discontinuations due to these AEs is shown in the solid bars. On the left are the results of our Phase IIb/III OA studies, and on the right are the results from VIGOR. By showing the results of our Phase IIb/III OA studies and VIGOR side by side, I am not trying to make direct statistical comparisons. Rather, the results of the Phase IIb/III studies are provided to determine whether the VIGOR results were generally consistent with current labeling.

Edema can occasionally be associated with NSAIDs and COX-2 inhibitors. Usually these AEs are minor clinical importance. They often resolve without a change in medication, and only rarely do they lead to discontinuation of the study drug. I am showing you here lower extremity edema because in our database the majority of edema-related AEs are reported as lower extremity edema, and lower extremity edema is the AE that is reflected in our label.

In the Phase IIb/III studies, as you can see, the 12.5 and 25 mg dose the incidence was similar to the NSAID comparators. Discontinuation rates in all doses were unusual but there was a dose-related increase at the 50 mg dose. The results of VIGOR were similar to what was seen in our Phase IIb/III studies and although the overall incidence of these AEs was actually slightly less than in the Phase IIb/III studies, despite the longer duration of VIGOR, it was, as you can see, slightly higher than the naproxen group and discontinuations were also numerically higher than naproxen but did not reach statistical significance.

[Slide]

This slide illustrates the incidence of hypertensive adverse experiences and, again, in the Phase IIb/III studies at 12.5 and 25 mg the incidence was similar to that seen with the NSAID comparators. There was an increase at the 50 mg dose; similarly in VIGOR, at 50 mg, two times our maximum dose, higher incidence compared to a commonly used dose of naproxen, likely related to the dose disparity between those. Discontinuations were also greater on rofecoxib, although at a low rate, 0.7 percent, compared to naproxen and this did reach statistical significance.

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The effects of COX-2 inhibition on renal sodium handling can rarely lead to congestive heart failure, and in both our Phase IIb/III OA studies and in VIGOR there was a low incidence of these events. The majority of these events did not lead to discontinuation of the study drug. In fact, in our Phase IIb/III OA studies there were really so few events that in order to make any sort of meaningful comparisons we have combined the rofecoxib and the NSAID groups her. You can see, in fact, that numerically there was a greater incidence of CHF adverse experiences in the combined NSAID group. This did not reach statistical significance. In VIGOR there was a numerically greater incidence of congestive heart failure incidence but, again, overall quite low, about 4 percent compared with naproxen which was about 2.2 percent.

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NSAIDs can rarely cause deterioration in renal or hepatic function, and to evaluate these potential adverse differences we evaluated discontinuations due to related AEs, as well as changes in renal or live chemistries which fell outside predefined limits of change. Discontinuations related to renal function of hepatic function occurred at a low incidence and were similar between the two groups. There was one death in the naproxen group due to hepatic failure and, in fact, that patient was considered a completer and is not counted in this analysis.

[Slide]

The predefined limits of change analyzed in this study included patients with lab changes on two consecutive occasions or on one occasion and associated with discontinuation. The predefined limits of changes for serum creatinine was an increase of 0.5 mg/dL from baseline and more than the upper limit of normal, and the increases in ALT -- the predefined limits were equal to or more than three times the upper limit of normal. As you can see, the percent of patients meeting these predefined limits of change was quite low in both treatment groups.

[Slide]

In summary, the VIGOR general safety results were similar to the results from our Phase IIb/III studies. Overall, rofecoxib was generally well tolerated and demonstrated a superior GI tolerability compared with non-selective NSAIDs.

The incidence of adverse experiences related to sodium retention, such as edema and hypertension, are similar to NSAIDs within the clinical dose range. However, these averse experiences are dose related, and with dosages above our maximum chronic dose there is an increase in these. Discontinuations at any dose, however, are rare and adverse experiences related to a decrease in renal function as well are rare and similar to NSAIDs.

Increases in liver function tests in patients on rofecoxib are similar to naproxen and ibuprofen and lower than those seen with diclofenac.

[Slide]

The one area where VIGOR demonstrated results which were different than those seen in the Phase IIb/III studies was in cardiovascular safety. When I refer to cardiovascular safety I am specifically referring to the incidence of thrombotic events, such as myocardial infarctions and cerebral vascular accidents. This is separate and distinct from renal-related AEs, such as edema and hypertension which were just reviewed and are dose-related, mechanism-dependent side effects.

[Slide]

Before I present the VIGOR cardiovascular results I want to take a moment to review with you the data that Dr. Nies previously presented to you on the effects of NSAIDs and selective COX-2 inhibitors on thromboxane and prostacyclin formation, and the questions that these data raised.

First, as you know, aspirin is an irreversible inhibitor of COX-1 and mediates near complete inhibition of platelet aggregation throughout its entire dosing interval.

While all non-selective NSAIDs inhibit platelet aggregation, most non-selective NSAIDs do not produce sustained inhibition of platelet aggregation. Naproxen, however, does inhibit platelet aggregation by about 90 percent throughout its entire dosing interval, and the magnitude of that effect is similar to that seen with aspirin. On the other hand, COX-2 selective inhibitors do not inhibit platelet aggregation. Both non-selective NSAIDs and COX-2 inhibitors do reduce secretion of urinary metabolite prostacyclin by 40-70 percent and the clinical significance of this is not known.

[Slide]

This data raises the following question, by inhibiting platelet function, can some NSAIDs have aspirin-like cardioprotective properties and would you expect there to be differences between the NSAIDs based on the ratio of COX-1 to COX-2 inhibition in the pharmacokinetics of the drugs? On the other hand, what are the clinical implications of inhibition of systemic prostacyclin synthesis without anti-platelet activity?

To address these issues, a standard operating procedure was established after the completion of the Phase IIb/III OA studies and prior to VIGOR to capture and adjudicate cardiovascular events in all COX-2 inhibitor studies.

[Slide]

Just as I did for you with the GI events, I just want to take a moment to review the definitions of some of the cardiovascular endpoints that I will be referring to. Again, these are thrombotic serious cardiovascular events. The first are confirmed thrombotic cardiovascular events. So, these are events that were confirmed as being thrombotic events by a blinded cardiovascular adjudication committee, and they include events such as myocardial infarctions, strokes, transient ischemic attacks, unstable angina and deep vein thrombosis.

The second are investigator reported thrombotic cardiovascular events. These represent the larger group of unadjudicated thrombotic events as reported by the investigators. So, in essence, these are unadjudicated events.

Lastly, is the APTC endpoint, which is the combined endpoint used by the anti-platelet trials collaboration. This is the most common and widely accepted endpoint used to quantify the overall cardiovascular impact of antithrombotic compounds in cardiovascular trials. This endpoint, which measures fatal and irreversible morbid cardiovascular events, is the combined incidence of cardiovascular and unknown cause of death, and it does include hemorrhagic deaths, myocardial infarctions and cerebral vascular accidents. This is considered the gold standard endpoint for the analyses of thrombotic cardiovascular events.

[Slide]

I am going to start the review of cardiovascular safety with the VIGOR results which did demonstrate a significantly reduced incidence of thrombotic adverse events on naproxen compared to rofecoxib. However, to further understand the reason for the difference between these two treatment groups, we examined in detail the results from both our Phase IIb/III OA studies which compared rofecoxib to placebo and NSAIDs without sustained anti-platelet activity, as well as from two large, ongoing placebo-controlled studies in elderly patients with Alzheimer's and mild cognitive impairment. Lastly, we performed a formal meta-analysis of cardiovascular results from all of our Phase IIb through V rofecoxib clinical trials.

The totality of data from these analyses demonstrated that the risk of sustaining a cardiovascular event on rofecoxib is similar to placebo and to NSAIDs without sustained anti-platelet activity. The reduction in events on naproxen compared with rofecoxib appears to be the outlier.

[Slide]

In VIGOR there were 45 confirmed thrombotic events on rofecoxib compared to 19 on naproxen. The relative risk of sustaining a thrombotic event on naproxen compared to rofecoxib was 0.42. The 95 percent confidence intervals you see here do not cross 1 and that implies statistical significance. Although there was a reduction in confirmed cardiovascular events, the cardiovascular mortality was low and similar in the two groups.

Now, if you break down the events by location, what you can see is that the majority of events were cardiac events and the majority of the reduction was in cardiac events. In the cardiac event category most of the events were myocardial infarctions and there was, in fact, a significant reduction in myocardial infarctions in the naproxen group compared to the rofecoxib group.

To better understand these results, we looked at the clinical characteristics of patients with events and we found that the patients who had thrombotic events were those who you would have expected to have thrombotic events. They were older than the overall cohort. Higher percentage of them were males, and close to 80 percent had one or more cardiovascular risk factors.

[Slide]

In addition, we explored any possible association between hypertension and cardiovascular events. NSAIDs and COX-2 inhibitors are both associated with small increases in systolic blood pressure and, as I noted earlier, there was a higher incidence of hypertension adverse experiences on rofecoxib compared to naproxen. Therefore, although it wasn't unexpected that small increases in blood pressure in this one-year study could explain the imbalance in cardiovascular events, it was important that we investigated any potential interaction and none was found.

We looked at patients with confirmed cardiovascular events to determine how many were preceded by a hypertensive adverse experience. Of the 45 patients on rofecoxib who had a confirmed cardiovascular event, only four had an antecedent hypertensive adverse experience and, as you can see, one had a deep vein thrombosis, two had cerebral vascular accidents, one had a myocardial infarction. In addition, overall changes in blood pressure were similar in rofecoxib patients who had cardiovascular events compared with patients who did not have cardiovascular events.

[Slide]

So, in VIGOR there was a significantly decreased incidence of serious thrombotic cardiovascular events on naproxen compared to rofecoxib. However, when you review the results of VIGOR in isolation you don't know whether the imbalance of cardiovascular events was caused by a decrease in events on a platelet-inhibiting NSAID, naproxen, or an increase in events on a COX-2 selective inhibitor due to inhibition of prostacyclin without concomitant anti-platelet effects.

[Slide]

The best way to differentiate between those two possibilities was to examine the cardiovascular results in the rest of the rofecoxib development program where rofecoxib was compared to other NSAIDs and, most importantly, to placebo.

[Slide]

In the combined Phase IIb/III OA studies, again, the treatment groups were rofecoxib, the combined NSAID group and placebo. Again, the combined NSAID group was diclofenac, ibuprofen and nabumetone, most of the experience being in diclofenac and ibuprofen. None of these maintained more than 90 percent inhibition of platelet aggregation throughout the entire dosing interval and, therefore, you would not expect them to be effective antithrombotic agents.

[Slide]

The incidence of investigator reported cardiovascular events is presented here as rates per 100 patient years, with the number of events in parentheses next to these. The rate of events on rofecoxib, as you can see, in these studies was 2 versus 2.3 events per 100 patient years in the combined NSAID group, and in those studies which had placebo the incidence of events was again similar, 2.5 versus 2.4. As you can see, the overall incidence of events was relatively low.

I just want to point out that I switched to investigator reported cardiovascular events, and the reason that I had to do that is that the cardiovascular SOP was instituted after the completion of these studies. But what we saw in VIGOR was that the investigator reported events were very similar to confirmed events. Both had about a 50 percent reduction on naproxen compared to rofecoxib.

[Slide]

On the vertical axis here is the cumulative incidence of investigator reported cardiovascular events, with time on the X axis. In blue is the NSAID comparison group from OA. In yellow is the rofecoxib group.

I am now going to overlay on that the results from the VIGOR study. In yellow, again, is rofecoxib from VIGOR and down here you see naproxen, and what you see is that the outlier here is naproxen, which is lower than any of the other treatment groups.

[Slide]

The results of the Phase IIb/III studies demonstrated that the risk of sustaining a cardiovascular event was similar on rofecoxib compared to NSAIDs without sustained anti-platelet effects, as well as to placebo but, as I pointed out, the amount of placebo-controlled data in the OA database is relatively small and, therefore, the Alzheimer's studies were important because they provide extensive long-term placebo-controlled data in the elderly patient population. Thus, these studies provide very informative data on the safety profile of rofecoxib compared to placebo.

[Slide]

We did a combined analysis of two large studies. The patient populations in the studies are similar. Again, this is an interim analysis. The treatment groups in these studies are 25 mg of rofecoxib versus placebo. And, we say high risk in that this is an elderly patient population. The mean age of the patients was 75 years of age. The majority of the patients were male. Over 50 percent had one or more cardiovascular risk factors. As of September, 2000 there were over 1000 patients and over 1200 patient years in each treatment group, with a median duration of therapy of 12.5 months.

[Slide]

Again, I am reporting here investigator reported events; number of events over here; rates of events over here. For rofecoxib you can see 2.8, 3.3 on placebo. We just recently received the results of confirmed events that were recently reported by the adjudication committee and, in fact, the results are quite similar with, again, a small numerical increase in events on placebo compared to rofecoxib but statistically similar.

[Slide]

The incidence of investigator reported cardiovascular events over time is illustrated on this slide. The visual impression is that there is an increase in event rate, especially at the end of the curve and especially in the placebo group. Something similar was seen in the VIGOR study in the rofecoxib treatment group. It is important to remember that as patient exposure diminishes as you go out here, the cumulative incidence estimates become much less precise. In all of these studies -- VIGOR and the Phase IIb/III studies, as well as in the Alzheimer's studies -- there was a constant relative risk over time. Again, I just want people to realize that white, here, is placebo; yellow, here, is rofecoxib.

[Slide]

As I noted earlier, the gold standard endpoint for assessing cardiovascular impact of antithrombotic agents is the combined APTC endpoint. This slide shows the relative risk, in diamonds, with 95 percent confidence intervals of sustaining an APTC endpoint on comparator versus rofecoxib. Triangles that fall to the left of 1 favor the comparator agent. Triangles which fall to the right favor rofecoxib.

The relative risk of sustaining an APTC endpoint, you can see in the Phase IIb/III studies where non-naproxen NSAIDs are compared to rofecoxib, is not statistically different between the two groups. Numerically, if anything, it favored rofecoxib and, again, in the Alzheimer's placebo-controlled studies there was no difference between the two groups. The outlier here is the naproxen data versus rofecoxib from the VIGOR study, which favored naproxen with a reduced incidence of events.

[Slide]

One way to put together the cardiovascular data across all of the studies is to do a meta-analysis. This meta-analysis included all of our Phase IIb through V studies which were completed by September, 2000 and were four weeks or more in duration. The exception here, again, is the Alzheimer's studies which are still ongoing, for which interim data was used. The APTC endpoint which, as I said, is the gold standard was chosen as the predefined endpoint for the meta-analysis.

[Slide]

This meta-analysis includes data on over 28,000 patients and over 14,000 patient years. Therefore, it ensures both power and precision.

[Slide]

The results of the meta-analysis confirm the cardiovascular results that I just showed you for VIGOR, the Phase IIb/III OA studies and the Alzheimer's studies. Again, you see the comparisons to placebo and non-naproxen NSAIDs, and the outlier here is the comparison to naproxen.

Now, since this meta-analysis combines studies of varying duration and dose of rofecoxib, a series of sensitivity analyses were done at the request of the FDA to see if either of these variables impacted the overall results.

[Slide]

To ensure that studies of short duration did not unduly influence the results, the meta-analysis was repeated using studies of six months or more in duration, and the results look almost identical to those I just showed you.

[Slide]

In addition, we evaluated the effect of rofecoxib dose. This latter analysis was limited by small numbers of events, however, a dose relationship was not observed. To evaluate this you can only combine studies in which each of the treatments was evaluated, and there was only one small study which had all three treatment groups, 12.5, 25 and 50, and, therefore, we combined studies that had both 12.5 and 25, over here, and 25 and 50 and, again, no apparent dose relationship was observed.

So, how can the cardiovascular results of rofecoxib compared to naproxen in VIGOR be reconciled with the results compared to placebo or non-naproxen NSAIDs? In aggregate, the clinical pharmacology data and clinical study data shown in the last several slides are consistent, with the explanation that in VIGOR the imbalance in cardiovascular events was due to naproxen reducing the risk of sustaining an event rather than rofecoxib increasing the risk.

[Slide]

Given these results, we were interested in determining whether there was any in vivo evidence in VIGOR of naproxen's ability to inhibit platelet function. Aspirin's effects on platelet function lead to an increased risk of minor bleeding events, such as epistaxis and ecchymoses, as Dr. Nies just mentioned, and in VIGOR naproxen was associated with a two- to three-fold increase in both ecchymoses and epistaxis compared to rofecoxib. Thus, there was in vivo evidence of naproxen's effect on platelet function.

[Slide]

Before I summarize the data presented by both Dr. Nies and myself this morning, I want to take a moment to review with you the data which does support naproxen's ability to act as an anti-platelet agent. The results of recently completed animal studies which have not yet been fully reviewed by the FDA, in an animal monkey model of acute thrombosis, have demonstrated that naproxen does have an antithrombotic effect which is similar to aspirin. We can show you the results of those later today.

As we have already shown you, the clinical pharmacology data shows that naproxen has sustained anti-platelet effects throughout its dosing interval, and these effects are different than those that are seen with ibuprofen. It also has aspirin-like increases in bleeding time. If you look at the naproxen label, which is actually different than either the ibuprofen or diclofenac label, it specifically states that naproxen increases bleeding time. Although there are no randomized clinical studies which have evaluated naproxen's ability to act as a cardioprotective agent, there is evidence from randomized clinical controls of other reversible, non-selective inhibitors which are potent anti-platelet agents, and these include studies with indobufen which is approved in countries outside of United States as a cardioprotective agent, not as an anti-inflammatory agent, and this agent has been shown to decrease graft occlusion and decrease thromboembolic events. In addition, flurbiprofen has been shown in one study to decrease the rate of recurrent MI by 70 percent compared to placebo.

Secondly, if you look at the incidence of cardiovascular events or myocardial infarctions across all of our treatment arms and all of our other databases, the rates are similar. Lastly, as I just showed you, there was an increased incidence with aspirin-like bleeding adverse experiences in VIGOR, which goes along with the anti-platelet activity that we think naproxen has.

We have also recently completed an epidemiologic study in the Great Britain general practice database. The results of this have only recently been shared with the agency since we just received approval from the external review board of that database to share these results publicly. But, this study did demonstrate a significant reduction in the risk of sustaining a thrombotic event in patients with rheumatoid arthritis who were treated with naproxen. Thus, there is substantial data which supports naproxen's ability to act as a cardioprotective agent.

[Slide]

In summary, rofecoxib is a COX-2 inhibitor without effects on COX-1 at and above the clinical doses. It demonstrates analgesic and analgesic and anti-inflammatory efficacy similar to non-selective NSAIDs in OA in acute pain, but it is associated with significantly fewer clinically important GI events compared with non-selective NSAIDs. This has been demonstrated independently in OA and in RA. We have seen consistent significant reductions in all endpoints, consistent significant reductions in high and low risk subgroups, and all of these results have shown that, in fact, endoscopic studies do translate into clinical GI outcomes.

[Slide]

Rofecoxib is generally well tolerated. The renal effects of rofecoxib and COX-2 inhibitors are similar to non-selective NSAIDs, are consistent with our currently approved labeling. Discontinuations are rare, and differences that were seen in VIGOR between 50 mg rofecoxib dose and 1000 mg naproxen dose, in mechanism-based, dose-dependent adverse events are consistent with the dose disparity. Lastly, there was a low incidence of transaminase elevations associated with rofecoxib.

[Slide]

In terms of cardiovascular safety, the risk of cardiovascular events on rofecoxib are similar to placebo and NSAIDs without sustained and nearly complete inhibition of platelet function, and the decreased cardiovascular events with naproxen in VIGOR is consistent with its potent anti-platelet effects. All of these cardiovascular results are consistent with rofecoxib's COX-2 selective and, therefore, its lack of anti-platelet activity.

[Slide]

This development program has clearly demonstrated that the COX-2 selective inhibitor rofecoxib has efficacy similar to NSAIDs but with a significantly improved GI safety profile. Its effects on renal sodium handling are similar to NSAIDs and the risk for sustaining a thrombotic event is similar to placebo.

The COX-2 hypothesis has been confirmed, and we believe that these data warrant modification to the current rofecoxib label to distinguish the GI safety profile of rofecoxib compared to non-selective NSAIDs. Thank you.

DR. HARRIS: I am going to ask the committee, because that was a lot of data that was presented, whether or not there are any questions to clarify -- any questions of clarity? There are several hands. I am going to start on my right today. Dr. Elashoff?

DR. ELASHOFF: Yes, I have questions about four slides. The first is 96, and what I wanted is standard errors, standard deviations, confidence intervals, any kind of indication of variability in those and in the comparison between them.

DR. REICIN: There were no substantial differences in those. You can see they were virtually identical, and I do not have a slide with standard errors but we can provide those to you.

DR. ELASHOFF: Okay. The next is slide 115, where there is a statement made about changes from baseline blood pressure that were similar, and I would like to see standard errors or confidence intervals for that statement.

DR. REICIN: We did a variety of analyses and, again, you know, you are talking about few events and so I am sure the standard errors are large. I don't have a slide with that. We looked both at changes from baseline and we also looked at patients who had predefined limits of change.

DR. ELASHOFF: Because means might appear to be similar but you have a huge confidence interval so that you can't make much of it.

Slide 120, I would like to see a version of that slide with the different NSAIDs broken down and the different doses of rofecoxib broken down.

DR. REICIN: There were too few events to break that out like that. We do not have a survival analysis done in that way.

DR. ELASHOFF: And, slide 127, I didn't pick up the distinction between thrombotic cardiovascular events and APTC events.

DR. REICIN: Sure, the major distinction between those is that thrombotic events include transient ischemic attacks, unstable angina, deep vein thrombosis, arterial thrombosis. Those are not included in the APTC endpoint. In addition, the APTC endpoint includes unknown cause of death, which is not included in the thrombotic endpoint, and it also includes hemorrhagic death.

DR. ELASHOFF: Thank you.

DR. HARRIS: Dr. Harell, I will give you a chance since we are moving right to left.

DR. HARRELL: I have two issues. One is on slide 89. In looking at the CV safety you were pretty quick to bring in other comparators and breakouts. I would like to see a breakout of the comparators on this slide.

DR. REICIN: Dr. Simon, do you want to come up?

DR. SIMON: Sure. Tom Simon, GI research at Merck.

[Slide]

What this slide represents is a combined analysis of the Phase IIb/III studies looking at GI endpoints. The trial was prospectively defined to compare NSAIDs as a group against rofecoxib, all doses combined as a group, and that is because all of those studies had at least one dose of rofecoxib and one of the NSAIDs. So, that is how the study was constructed and those are the main results.

One of the problems you have when you breakout the NSAIDs individually is that there is confounding by protocol type. Not every type of protocol -- there were endoscopy studies, short-term studies and long-term studies and not every NSAID is represented in every type of protocol. So, when you look at them separately there is this caveat around it.

[Slide]

Just to show you the data since you asked, I would like to start with the diclofenac results. What we have done here is to break diclofenac out of the studies, and you can see that numerically there is a trend in favor of rofecoxib. The point estimate for the relative risk reduction is 0.86, however, the confidence interval is broad because the number of patient years is small. That is true when you look at the confirmed PUB events, which is the primary endpoint, and also true when you look at the secondary endpoint.

DR. ELASHOFF: Dose of rofecoxib?

DR. SIMON: That is all doses combined. Looking at the confirmed plus unconfirmed events, there is again the same trend.

[Slide]

This is looking at ibuprofen and you can see that the difference between rofecoxib doses combined and ibuprofen is larger. That relative risk is shown here, again, less than 1 in favor of rofecoxib and the confidence intervals are also illustrated.

[Slide]

Lastly, I would like to show you slide 80. What this illustrates is some of the consistency of the results favoring rofecoxib. This is the result with all protocols combined, looking at rofecoxib doses combined versus NSAIDs. What has been done here is that each of the individual protocol types has been removed serially to show you what the results look like when you take out the different types of protocol. This is protocol 029. This is an ibuprofen study. When you take it out the result is consistent. This is also with ibuprofen taken out and the result is consistent. This is a diclofenac study. These are the OA efficacy studies When you take those out the results are also consistent favoring rofecoxib. Finally, when you take out the endoscopy studies you get a point estimate that favors rofecoxib as well. This last study is a nabumetone trial again and if you take that out the results are still consistent.

DR. HARRELL: Thank you. My second question is at some point during the VIGOR study, presumably the DSMB saw a significant difference in serious CV event rates, yet they didn't stop the study. What were the operating procedures that were in effect, or what documentation did the DSMB have regarding this point?

DR. REICIN: I think I am going to have Dr. Neaton answer that question. Dr. Neaton was a member of the DSMB and since I was not privy to those meetings I think it is most appropriate for him to answer those questions.

DR. NEATON: Maybe I can try to answer it and then you can be more specific with your question. We reviewed the data analysis plan in advance of reviewing the data and approved that, and we met three times during the fall of 1999. The first analysis was preplanned to look at the GI toxicities. The criteria were both for PUBs and complicated PUBs. The PUB criteria were met, the complicated was not. It was close. Because during the discussions of the data analysis plan, of the design of the study, a great deal of emphasis was placed on the complicated and even though it was close we decided to continue. We noticed at that point a trend for the cardiovascular events and requested additional analyses, and those were reviewed on two different occasions, later, I believe, in November and again in December. The additional analyses requested were primarily to take advantage, to the extent we could, of the different sources of data that were being presented to us on discontinuations, on adverse events coming from different databases.

You are correct, there was a nominally significant difference in cardiovascular events, I believe, even on the second occasion when we reviewed it, but these were unadjudicated events and we were combining the events in a way that we felt was relevant. We felt ultimately that it was probably in terms of continuing this trial to get more definitive data on precisely the nature of the cardiovascular events and the differences between the two treatment groups to balance that against what we were seeing or, rather substantial efficacy or reduction in the GI toxicities. So, at our last meeting, which was close to the time when the trial was scheduled to end, we requested that the events for VIGOR be adjudicated. There was an adjudication protocol that we were made aware of in the pre-study planning and design. But, we were not clear that the timetable for the adjudication of those events was in sync with the completion of the VIGOR study. So, we felt that to properly balance kind of the positive and negative sides of treatment A versus treatment B, we felt that those should be adjudicated before the results were unblinded. So, we made that request at our last meeting.

But, the DSMB was provided information by the study statistician, Dr. Shapiro. We reviewed that information. They were very responsive to every request we made for additional data. From that point of view, the information we received was outstanding and the responsiveness was outstanding.

DR. HARRELL: Was the DSMB blinded throughout this process?

DR. NEATON: The DSMB was blinded. We chose up front that the treatments would be coded A and B. However, after the first look, as in most cases, we anticipated probably what the results were. So, we never really requested to be unblinded but I think it is probably fair to say that we had a notion of which way the results were going.

DR. HARRELL: And, did the DSMB have any written minutes about reasons for not terminating the study?

DR. NEATON: For not terminating the study -- I think probably there were a variety of reasons in all of our minds. One of them had to do with something I mentioned earlier about specifically how to combine the serious cardiovascular events. They were broken down individually and we basically chose to combine them in groups that we thought were relevant, as well as kind of to try to merge what were recorded as adverse events and reasons for discontinuation. There was a small excess of deaths on treatment A that was not significant. The most serious event that you might consider was a little worrisome but was not so pronounced -- and the numbers were very small. More generally, for the major cardiovascular events, the numbers were small and were unadjudicated.

So, I think that there was speculation on the part of some people on the board that this could be a protective effect of naproxen, treatment B as we referred to it at the time. I don't think that was the reason for our allowing it to continue. At least personally, and I think other people shared this, it was to get more definitive information on this because we felt it would be an important thing to have good data both on these cardiovascular events and GI events, and while we have superb adjudicated data on GI events, the data on the cardiovascular events were coming from different databases and we felt that they should be kind of collected and presented ultimately in the same quality as the GI events.

DR. HARRELL: Thank you.

DR. REICIN: Dr. Elashoff, on page 27 of the background package, Table 6 for the efficacy measurements, you can see standard deviations and 95 percent confidence intervals. Standard errors are not on that table but for all three efficacy endpoints the standard errors were 0.015.

DR. ELASHOFF: Pardon me, I wasn't listening quick enough. It is Table 6, which I just found --

DR. REICIN: Right, the standard errors are not provided in that table. It is standard deviations in that table. The standard errors were 0.015.

DR. ELASHOFF: Thank you.

DR. SAMPSON: Allan Sampson. I wanted to follow-up on Dr. Harrell's question about slide 89. Maybe it is in the background document, but do you have that for the complicated upper GI events, the so-called POBs? That is for POBs, right?

DR. REICIN: This is for POBs. I think there were only nine complicated events in the study.

DR. SIMON: I don't have that broken out by dose but the problem is there is only a small number of PUBs.

[Slide]

What you are looking at here is the incidence of perforations, obstructions and bleeds that occur over time. I actually don't know which NSAIDs those are on but we felt that the numbers were so small that we didn't break them out separately.

DR. SAMPSON: Second question, there was slide 41 on platelet aggregation, naproxen versus ibuprofen, and that was truncated at 8 hours. Since one is a t.i.d. dosing and one is b.i.d. dosing, would you have that going out to 12 hours?

DR. NIES: Yes, as I explained when I began, this is at steady state. This is after 5 days of dosing. The first point is 12 hours after the previous dose. So, that is the 12-hour time point for naproxen. It is the 8-hour time point for ibuprofen. We do have another 8-hour time point at the end of the dosing interval for ibuprofen. For naproxen we didn't go out another 12 hours. But we assumed, since the 12 hours from the previous dose was already completely inhibited, it would stay that way.

DR. SAMPSON: I understand. Thank you. I have one other question. There was something we say yesterday that was an interesting summary, and that was the incidence of significant hematocrit and hemoglobin drops, and I think it was defined by hematocrit less than 10 percent and hemoglobin less than 2 gm. Do you have a comparison on that that you could show us?

DR. REICIN: Yes, we do.

[Slide]

As you see, there was a numeric trend. It did not reach statistical significance for rofecoxib compared to naproxen. I think part of this is that you have fluid retention also having an impact here. As Dr. Nies mentioned, we have studies which have actually looked at clinical GI blood loss, giving patients tagged red blood cells, and that has shown a significant reduction in subclinical GI blood loss. In fact, in our Phase IIb/III OA studies, at the 25 mg dose we did see a significant reduction in those type of hemoglobin/hematocrit changes but at the 50 mg dose, because of fluid retention, the differences are diminished.

You can see here a decrease in hemoglobin of more than 2 g/dL and hematocrit of more than 5 percent, or hemoglobin or more than 1 drop, or a hematocrit drop of more than 10 percent, there at the bottom. You can see numeric trends but this did not reach statistical significance.

DR. SAMPSON: Thank you. One final, more technical question for my own clarification, VIGOR was run under two separate protocol, 88 and 89 --

DR. REICIN: That was an administrative issue because one protocol was outside the U.S. and one was in the U.S. The started at exactly the same time. The protocols were identical. Everything was handled -- there was one database. The endpoints came in, in the same way. It was merely administrative.

DR. SAMPSON: But, as I understand it, one was restricted to sites in the U.S. and one was sites internationally.

DR. REICIN: Correct, and because of the way we conduct studies outside the U.S. it had to be under a separate protocol number.

DR. SAMPSON: Were there analyses done -- I have no access to these -- that looked at the protocols separately, looking both at potential effects or differences due to sites in the U.S. versus ex-U.S.?

DR. REICIN: We did both our GI analysis and our cardiovascular analysis that way, and we had basically similar results both in the U.S. and outside the U.S.

DR. SAMPSON: Thank you.

DR. HARRIS: Dr. Wofsy?

DR. WOFSY: Thank you, my question has been asked and answered.

DR. HARRIS: We will go around the table. Yes?

DR. PINA: I need several clarification points about your comparison group of IIb and III. Were group II healthy volunteers?

DR. REICIN: IIb, no. The IIb are dose-ranging studies in osteoarthritis. So, the IIb/III studies are all osteoarthritis patients. All those protocols had very similar inclusion and exclusion criteria.

DR. PINA: Do you have a comparison of the patient population demographics --

DR. REICIN: I do.

DR. PINA: -- between those and VIGOR?

DR. REICIN: Yes, I do.

DR. PINA: I would be interested to see if the populations are different.

You will see they were not exactly the same but similar, as we are looking for the slide. The mean age in VIGOR was about 58. The mean age in the Phase IIb/III OA studies was 62.

[Slide]

There were, I think, about 7 percent more males. You can see the Phase IIb/III results over here, on the left and VIGOR on the right. You can see the percent of patients with any cardiovascular risk factor is similar, not exactly identical, and past history of atherosclerotic disease is similar, not identical.

DR. PINA: Was the decision to enter patients based on their need for concomitant aspirin left up to the individual investigator in VIGOR?

DR. REICIN: Yes, it was. We specifically in the protocol told people not to take patients off aspirin in order to allow them to enter the study.

DR. PINA: And, what was your definition of hypertension?

DR. REICIN: That is left up to the investigators. So, it is reported on the past medical history form, and adverse experiences during the study are, again, reported by the investigators.

DR. PINA: But was there a definition for this event since you were capturing hypertension?

DR. REICIN: There was no definition for it.

DR. PINA: Then, one last question, of the patients who had ecchymoses as you are using ecchymoses as a sign of platelet dysfunction, how many of those patients were on steroids?

DR. REICIN: We didn't do that analysis.

DR. PINA: You had a certain number of patients on steroids --

DR. REICIN: Over 50 percent of patients were on steroids. It is actually an interesting question.

DR. WOLFE: I have a few questions.

DR. HARRIS: Can you just say your name into the microphone?

DR. WOLFE: I am sorry, Michael Wolfe. I have a few questions. One comes back to the question of the IIb and III OA patients. Were they allowed to take a low dose of aspirin?

DR. REICIN: No, low dose aspirin was also not allowed in those studies, except for one very small study in the elderly that maybe makes up 100 of the patients.

DR. WOLFE: Speaking of small numbers, you showed some of the data comparing rofecoxib with diclofenac and ibuprofen, but do you have any comparison -- again, I am sure the numbers are very small -- of rofecoxib versus nabumetone?

DR. REICIN: Yes, we do, and you are asking specifically about --

DR. WOLFE: The number of POBs or PUBs.

DR. REICIN: In our nabumetone studies there were no endpoints in any of the groups.

DR. WOLFE: Too small.

DR. REICIN: Yes. That is why I tried to be very clear in my talk to say that really most of the experience was on diclofenac in that regard.

DR. WOLFE: I have another question regarding the H-2 blockers in VIGOR. I realize there is only over-the counter dosing but you mentioned dose creep, and there is certainly dose creep with H-2 blockers over-the-counter and one of your consultants has data suggesting that high dose of famotidine may be protective. Do you have any information on the amount of H-2 blockers used?

DR. REICIN: Yes, I do.

[Slide]

Slide 184 shows the use of GI co-medication -- this is any, so if you took one dose you count here -- during the study and, not surprisingly, H-2 blockers are used more than any of the others because they were allowed, and very low use of proton pump inhibitors.

DR. WOLFE: But do you have the amount? Did any of the patients take huge amounts of H-2 blockers? One dose is absolutely nothing. I personally think high doses don't do very much --

DR. REICIN: While I can't give you exact amounts, the majority of patients were on over-the-counter doses. There were a few that were taking higher doses, although we didn't look for super-therapeutic doses.

DR. SIMON: Tom Simon again just to make one point. If you want to prevent ulcers with an H-2 antagonist like famotidine, you have to go to, like, 80 mg a day for a sustained period of time. So, that probably wouldn't be consistent with the type of OTC H-2 use as permitted in VIGOR.

DR. WOLFE: You would think that but I am sure there are people out there who figure if two are good, three and four are probably even better.

DR. HARRIS: Dr. Cryer?

DR. CRYER: This continues along the line of questions comparing your Phase IIb/III and VIGOR results. You suggest that the GI event rate in your RA population was generalizable to a larger population because the relative risk reduction in your clinical GI events in VIGOR and your RA patients were similar to the IIb/III OA studies. However, as has been pointed out, the OA studies had an average dose of rofecoxib that was about 25 mg. The question is do you have an analysis of the event rate in your OA studies using just the 50 mg dose of rofecoxib?

DR. REICIN: Dr. Simon?

DR. SIMON: Actually, we have stayed away from that for the reasons that I mentioned earlier about not wanting to split the doses out separately. There isn't enough exposure in each of the doses to look at them consistently. The other problem you run into actually when you try to break up the dose-response curve, it ends up looking U-shaped and the placebo ends up being between the lowest rofecoxib dose and the highest rofecoxib dose, and that is part of why we think that method of analysis is just not a reliable way to look at the data.

[Slide]

I have indicated it is a little bit complicated but let me just take you through this. Here is what is happening, we have indicated that this analysis combined protocols of several different types. This is a Phase IIb/III dose-ranging study in OA. These are Phase III studies in OA. This is an endoscopy study and this is the elderly study.

The easiest thing to do probably is to look at the rate per 100 patient year columns. What you have to do if you mentally want to see what is going on with 50 is look at this column and this, and those look sort of high except that if you take a look at the 12.5 and then the placebo there is just an anomaly going on here. I think when you actually break the data out the numbers just start to get sparse when you try to stay consistent. That is the reason we have been leaning away from talking about 50 mg and how it compares to the other doses because the only data we have is just too sparsely populated when you look protocol type to accurately represent it.

DR. CRYER: I failed to introduce myself earlier, Byron Cryer. I only have one other question. Did you detect any OTC NSAID use in your VIGOR trial?

DR. REICIN: There was very low usage of over-the-counter NSAIDs.

DR. CRYER: And, did that affect the outcomes in any way?

DR. REICIN: No. In fact, as a part of our per-protocol analysis, patients who used NSAIDs for more than 14 days during the study were excluded from the per-protocol analysis, and for the per-protocol analysis the results were even stronger than the intention-to-treat analysis.

DR. HARRIS: Yes, Dr. Sampson?

DR. SAMPSON: One other question in trying to sort through the meta-analysis in the APTC. Do you have a breakdown, first of all, in RA patients excluding the VIGOR trial? Because what I would be interested in seeing is are there enough patients in RA taking naproxen that you can do another analysis that would give us a flavor, separate from VIGOR, of what it looked like in the other studies --

DR. REICIN: Yes. I will caveat by telling you that our entire Phase III program was done with naproxen as the comparison, and the RA results are mainly in VIGOR, but we did do an analysis in RA just specifically looking at the APTC endpoint. I am going to show that to you.

[Slide]

If you go to slide 289, this shows you the incidence of APTC events in our Phase IIb/III RA studies. The number of events is in parentheses, rates per 100 patient years, and I think the numbers speak for themselves. I mean, only two events on 12.5.

Were you interested in seeing the epidemiologic data that we have in patients with rheumatoid arthritis? Can I turn that over tc Dr. Guess to show you that data?

DR. SAMPSON: Sure.

DR. GUESS: These are some data from an analysis that we did in the U.K. general practice research database.

[Slide]

This is a large database in the United Kingdom that encompasses about 1500 general practitioners and about 3 million people, about 5 percent of the population of the U.K. It is a database that is owned by the Medicines Control agency and they license it out. We conducted a study, completed it and just got the approval of the scientific review committee about two days ago to share the preliminary results with you, and I will go through the analyses that we looked at.

[Slide]

The objective of the study was to determine whether current use of naproxen is associated with a lower risk of acute major thrombotic events among rheumatoid arthritis patients in the same age range we are looking at.

[Slide]

It was a case-control study among all of the 17,000 eligible RA patients in GPRD. There were approximately 38,000 total patients when you exclude the ones that are not in the age range, and when you look at the exclusions that we have here, it comes down to 17,000 patients, all of the patients with rheumatoid arthritis in the database. We excluded prior cardiovascular disease, cancer, vasculitis, coagulopathy, renal disease, liver failure, alcohol or drug abuse, aspirin, anticoagulants, and anti-platelet drugs. Controls, about 2000 of them, were matched to 720 cases on age, gender and medical practice, and there was adjustment for smoking, DMARDs, steroids, estrogen, diabetes, cardiovascular risk factors and other medical co-morbidities.

[Slide]

We took as a composite of acute myocardial infarction, sudden death and CVA, and it was like the APTC endpoint but it did not include hemorrhagic deaths or other forms of death. It was largely driven by the MI and the CVA. Only the first endpoint is looked at in a given analysis on a patient.

[Slide]

The exposure we had was current use of naproxen, as defined by a prescription for naproxen within the past 30 days prior to the index date, and the unexposed group were people that had not used naproxen within 365 days of the index date.

[Slide]

The preliminary results that we have here are that a current prescription for naproxen was associated with lower odds in an acute thromboembolic event than was known naproxen during the past year. The odds ratio was around 0.6 with a confidence interval that didn't include 1, and adjustment for confounders didn't really change the results.

So, in this epidemiologic database we saw for the first time that current use of naproxen does appear to be, in RA patients, associated with a decreased risk of thromboembolic events in a very preliminary analysis.

DR. SAMPSON: Thank you. I was just wondering if it would be possible to get the preceding slide that Dr. Reicin showed, just a hard copy of that at some point by lunch time.

DR. REICIN: Yes, sure.

DR. HARRIS: Just to ask if that is doable.

DR. REICIN: Yes, absolutely.

DR. HARRIS: Dr. Nissen?

DR. NISSEN: Could you provide the actual event rates from that U.K. data, not just the odds ratios?

DR. GUESS: It is a case-control study so there would not be incident rates. In other words, in a case-control study you select people that have cases with the event and then you pick controls and you see which of those fractions had exposure to the drug. So, you wouldn't be able to get incidence out of that event.

DR. NISSEN: There just isn't any data available?

DR. GUESS: Well, you could analyze this as a cohort study but one of the problems with analyzing this as a cohort study with three million records is that we had a very limited period of time to do that. We actually have that on our plate to do but the data set is enormous and we did not have time to complete that type of analysis. It is on the plate to do.

DR. HARRIS: Since this may be a cardiovascular related question, I am going to ask Dr. Pina to ask the question.

DR. PINA: Your studies 085 and 090, are they included in that IIb/III OA composite analysis?

DR. REICIN: They were not included in the IIb/III OA composite analysis. They are, however, included in the meta-analysis that I showed you with non-naproxen NSAIDs.

DR. PINA: You allowed aspirin in those two trials?

DR. REICIN: We did allow aspirin in those two trials.

DR. PINA: And in 090 there was a greater rate of thrombotic deaths in the rofecoxib group --

DR. REICIN: No deaths.

DR. PINA: No deaths?

DR. REICIN: Right.

DR. PINA: But thrombotic events?

DR. REICIN: Yes.

DR. PINA: Do you have that data?

DR. REICIN: What I can show you is the combined analysis we did from all of our aspirin users, looking in all of our studies that allowed aspirin. Can you go to slide 1639?

[Slide]

We had the two nabumetone studies that allowed aspirin. There was a small elderly study that allowed aspirin, a large advantage study that was a short-term study that also allowed aspirin, and also our Alzheimer's studies were amended recently to allow aspirin. So, this is an analysis we did looking at APTC endpoints in those that allowed concomitant aspirin.

What you can see is that the incidence of the APTC endpoints is almost identical in the two treatment groups, and then you look beneath it, patients who were not just in those studies taking concomitant aspirin.

DR. PINA: And then one last clarification, in your VIGOR trial toward the 8-month follow-up there seemed to be an acceleration of thrombotic events on your drug versus the naproxen. Do you have any explanation or any clarification about that?

DR. REICIN: As I mentioned when I showed you the placebo data with Alzheimer's, you saw almost that same type of acceleration out at the end of the curve there as well. Part of it is the visual impression of what you do with Kaplan-Meier curves. You have less people that have exposure as you go out, therefore, the estimates of the relative risk are much less precise out there. Statistically speaking though, we looked for constant relative risk over time and there was a constant relative risk over time.

DR. WOLFE: I have a cardiovascular question on VIGOR. If you exclude the people with a previous history of MI and/or high risk people in the analysis of thrombotic events do you see as big a difference between rofecoxib and naproxen?

DR. REICIN: You don't see as big a difference but you do still see a difference, and depending on the endpoint it sometimes reaches statistical significance and sometimes it doesn't. For MIs in particular it didn't, but the numerical trend is still there.

DR. HARRELL: A follow-up to that question, did you look at the traditional risk factor equations, like Framingham, and see if the risk factors operate the say way there?

DR. REICIN: You have to expand a little bit.

DR. HARRELL: So, if you put in your cardiovascular risk factors and age, and got the Framingham predicted risks and asked whether the Framingham risks predict the same way as they did in the Framingham population, or do risk factors in your study come in to have a different weight?

DR. REICIN: If I am understanding the question, all of the risk factors that you would expect to have higher event rates had higher event rates. So, older patients had higher event rates; males had higher event rates versus female patients with a history of hypocholesterolemia, higher event rates compared to those who did not. In each of those groups the relative risks were maintained. As I said, if you looked at the cohort of patients who had a confirmed event and you compared it to the entire VIGOR cohort, they were a higher risk patient population.

DR. HARRELL: And one step further, do the weights of the risk factors appear to be the same as risk equations that have been published in the literature?

DR. REICIN: We didn't do the analysis in that exact way.

DR. HARRIS: Dr. DeLap?

DR. DELAP: I just wanted to add one cautionary note about the epidemiology U.K. data that you saw just a couple of minutes ago. That is new data to us as well as to the committee, and we have not completed review of it. So, we are not confident at this time to say what we will or will not be able to conclude once we do complete our reviews of those data.

DR. REICIN: I did mention that in my talk.

DR. HARRIS: Thank you. Does that conclude your presentation?

DR. REICIN: It concludes my presentation.

DR. HARRIS: Thank you very much. We are running about half an hour over, however, I am sure we need a 15-minute break, which we will have. We will convene again at 10:45.

[Brief recess]

DR. HARRIS: I am calling the session back to order. We are now going to proceed with the FDA presentation, and we will start with Dr. Villalba providing a medical overview.

FDA Presentation

Medical Overview

DR. VILLALBA: Good afternoon, ladies and gentlemen, members of the advisory committee. My name is Lourdes Villalba, and I am a medical officer in the Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products.

[Slide]

We are here to talk about Vioxx Gastrointestinal Outcome Research, the VIGOR study. I won't be repeating many of the discussions that we had yesterday. Dr. Witter already gave you a background introduction and chronology of events related to the development of these protocols, and the sponsor has already presented in detail the VIGOR study. In this introduction, I just want to point out some issues that will be relevant for the afternoon discussion.

[Slide]

The VIGOR study was a large, randomized study with a follow-up of about nine months, and it was conducted to gather further information to characterize the GI safety profile of rofecoxib. Vioxx currently carries the GI warning label of the NSAID class and, based on this study, the sponsor proposes to downgrade the label and place a modified version under the precaution section of the label.

[Slide]

Now I would like to go straight to the issues that I want to discuss. First of all, treatment. The dose of rofecoxib used in the study was 50 mg a day. This is twice the upper dose labeled for chronic use in osteoarthritis, but it is also the dose approved for the treatment of acute pain. The dose of naproxen 500 mg b.i.d. is the maximum labeled dose for chronic use in osteoarthritis and rheumatoid arthritis, and the label states that a 1500 mg dose can be used for short term in OA and RA. Rofecoxib is not currently labeled for use in rheumatoid arthritis. The anticipated dose by the sponsor's studies would be 25 mg, but studies to support the safety of rofecoxib in rheumatoid arthritis have not been submitted to the agency.

[Slide]

Why the 50 mg dose? Well, the agency suggested or required this dose, twice the upper limit of their chronic dose, for both celebre and Vioxx, and the idea was to get a safety margin because if the product is perceived as being safer in the GI system, that organ-specific safety may be interpreted by some as general safety. Therefore, it is important to know what happens when patients go higher or above the dose that is recommended. And, we are aware of the dose creep phenomenon in chronic painful conditions.

The rofecoxib dose, as I said, is approved for the treatment of acute pain. The label states, under usage and administration, that Vioxx has not been studied for more than five days in pain studies. However, there is no limit for the use of the 50 mg dose and we may assume that some patients will take it for longer than five days.

[Slide]

In fact, we do have some postmarketing usage data, data provided by IMS Health from May '99 to September 2000, and of a total of approximately 13 million drug appearances in that data base, 650,000 were for the 50 mg trend and, of those, 21 percent were for more than 30 days. Therefore, we do have evidence that people take the 50 mg dose for longer periods than they are supposed to.

[Slide]

Regarding the population, this was a population of patients with RA and 70 percent of the patients were women. The median age was 58, and approximately 56 percent were on concomitant corticosteroids and, very important, an exclusion to this protocol was that low dose aspirin was not allowed. Patients on low dose aspirin were not supposed to stop to get into the trial. They were just not included. And, any patient deemed by the investigator to require prophylactic aspirin or anticoagulation at the time of screening was excluded.

[Slide]

I have moved to the next slide but I would like to make the point that that exclusion actually takes out a substantial number of patients ion the target population of osteoarthritis and rheumatoid arthritis who will be candidates for cardiovascular prophylaxis.

Regarding endpoints, this was a safety study. It had organ-specific endpoints and those will be discussed by Dr. Goldkind. The study was powered to detect a difference in GI specific endpoints but also included prespecified analysis of routine safety parameters and NSAID-related events, such as renal-related, liver-related, edema etc.

[Slide]

This was not an efficacy study. It was not designed as an efficacy study. It was a non-flare design. Change in disease-modifying antirheumatic drug therapy, systemic and intra-articular corticosteroids were allowed, and rescue analgesia with acetaminophen and non-NSAID was also allowed at the investigator's discretion. Therefore, it is not surprising that at the end there were no major differences in efficacy endpoints.

Also, some efficacy endpoints were included, such as patient and physician global assessment and modified HAK and the dropouts due to lack of efficacy, however, there was no measurement of swollen joints, tender joints, ESR/CRP -- those standard measurements in any rheumatoid arthritis trial for efficacy.

[Slide]

The major issues that we would like to discuss today are the generalizability of the gastrointestinal findings in patients on aspirin and generalizability of the findings to other NSAIDs, other than naproxen. The cardiovascular findings -- and we do have statistical issues with the meta-analysis presented by the sponsor, and also the fact that organ-specific safety cannot be generalized to overall safety.

The speakers for the FDA will be Dr. Larry Goldkind. He is a gastroenterologist and team leader in our division. Dr. Shari Targum will talk about the cardiovascular safety, and she is from the Division of Cardiorenal Products. Dr. Qian Li will discuss statistical issues, and I will come back at the end to talk about overall safety and conclusions.

Gastrointestinal Review

DR. GOLDKIND: Good morning.

[Slide]

I am Dr. Goldkind, and I will discuss the highlight of the VIGOR trial gastrointestinal review.

[Slide]

Briefly to outline my presentation, I will discuss study hypothesis and definition of endpoints, review of the results, some discussion of high risk populations, a brief discussion of the meta-analysis that was presented by the sponsor of IIb and III studies, and some conclusions.

[Slide]

Again, much of this is a repeat of what has been discussed. Organ-specific endpoints were defined although, again, it was a large trial and meant to capture overall safety as well as the organic-specific endpoints related to the underlying physiologic hypothesis.

PUBs, perforations, symptomatic ulcers and bleeding, was a primary hypothesis. Complicated PUBs, which excluded those ulcers presenting with symptoms only, was a second important study point. The statistical plan, again, was to include a minimum of 120 confirmed PUBs, 40 confirmed complicated PUBs and 6 months of enrollment following the last patient randomized. The power calculation was produced to detect a reduction in risk of at least 50 percent for the primary GI hypothesis.

[Slide]

That hypothesis, as stated in the protocol, was that the risk of confirmed PUBs during the treatment period will be reduced in the group of patients with rheumatoid arthritis taking 50 mg of Vioxx daily compared to the group of patients with rheumatoid arthritis taking naproxen 1000 mg daily. Vioxx, administered at a dose of 50 mg daily, will be safe and well tolerated.

[Slide]

The endpoints, to briefly review the definitions -- any one of the following four clinical presentations would be considered as a confirmed PUB: Ulcer, presenting with signs or symptoms, or both, would require radiographic, endoscopic or surgical confirmation. Perforation confirmed radiographically, endoscopically, surgically or at autopsy. Obstruction -- this required at least 24 hours of postprandial nausea and vomiting in addition to evidence of narrowing of the gastric outlet.

[Slide]

GI hemorrhage would require a healthcare provider witnessed episode of frank hematemesis, coffee ground emesis, NG aspiration of blood or coffee ground appearing gastric contents, melena, to be distinguished from other causes of dark stool, and active upper GI bleeding at the time of endoscopy, surgery or angiography.

[Slide]

In addition, heme-positive stool associated with a documented upper GI lesion, judged by the healthcare provider to be the source of GI bleeding, associated with a significant bleed or stigmata of recent bleed would also be considered an event and, again, a drop in hemoglobin of 2 g/dL or more, hypotension or the need for transfusion were required. These were rigorous definitions.

[Slide]

For a complicated event, any perforation and any obstruction would be included in that category. A gastric ulcer or duodenal ulcer, however, would only be included as a complicated event if there was a sign of substantial, potentially life-threatening associated. Again, this excluded symptomatic ulcers.

[Slide]

To briefly review the results, these have been shown previously, just formatted differently. Vioxx compared to naproxen, the rate, either per 100 patient years or cumulative rate, did show a rusk reduction, 0.46, with a highly statistical significant p value.

[Slide]

Complicated PUBs, again Vioxx compared to naproxen, showed a relative risk of 0.43, and these are the differences seen per 100 patient years as well as the cumulative rates. Not surprisingly, the cumulative rates, the absolute numbers are substantially less for complicated PUBs which was a more rigorously defined and rare endpoint, fortunately, than the simple PUBs.

[Slide]

Again, just to look at the types of confirmed PUBs, it was what one would expect looking at the literature. The majority were symptomatic ulcers, gastric and duodenal. A subset of these were upper GI bleeds, and perforations and obstructions were rare in the database.

[Slide]

Now moving on to subgroup analysis based on risk factor, looking at a prior history of PUB, as has been presented, the risk reduction is maintained across both risk categories. The point that I would like to make in this slide is that while the risk reduction is substantial and persists in the high risk group, the absolute rates, either per 100 patient years or accrued rate in this slide, here, is of note even in the Vioxx group. So that, while the relative risk in that population goes down, the absolute risk is actually quite significant and, compared to a lower risk population even on naproxen, again remains a significant event rate.

[Slide]

Looking at age as a risk factor, again the relative risk reduction is maintained both for the population under 65 and the population over 65 but, once again, the high risk group does continue to have absolute rate of events that are similar to the rate seen in the naproxen group in the lower risk population.

[Slide]

This slide will look familiar to a lot of people. If age and a history of PUB are independent risk factors for ulcer disease, then the findings of a high risk in association with therapy may simply represent the intrinsic risk associated with that population rather than any additive effect of the drug. So, there may be no causality between the drug and the added risk. On the other hand, there may well be an interaction between the underlying risk population and the drug such as to produce an exaggerated or a higher attributable risk to therapy.

[Slide]

So, the outstanding question related to the absolute rates of events that we saw in the previous slides is whether high risk patients should be treated with lower relative GI risk NSAIDs, or does the overall residual or absolute risk associated with usage continue to represent a contraindication for these patients? The answer to that, of course, involved clinical information related to the individual patient and the strength of the indication for treatment, and this question has obvious usage implications.

[Slide]

GI risk, again, in special populations -- other outstanding questions are the GI risk of co-administration of aspirin and Vioxx where further data is needed, the GI risk of co-administration of aspiring and Vioxx in the elderly where more information is needed, and the subpopulation of both elderly and a history of PUB -- what the GI risk in that population would be. Even this large database couldn't answer that question because of how small the intersection of elderly and history of PUB would be in terms of the numbers of patients enrolled.

[Slide]

In terms of the generalizability of GI safety, as the sponsor has noted, Vioxx did have a substantial decrease in risk for the PUBs and complicated PUBs, as noted here. In terms of the degree of absolute risk, a comparative database cannot answer that. Again, the issue of relative risk compared to other NSAIDs has been addressed to some extent by the sponsor although further data is needed.

[Slide]

I will briefly review the data that was presented from the IIb and III studies, which was a meta-analysis of PUBs using Vioxx at all three doses as one group versus NSAIDs as a composite group. It is important to note that three doses of Vioxx were used in this meta-analysis, 12.5, 25 as well as 50 mg, and although there was a third comparator, nabumetone, in the database the exposure was very small, and the next slide will only show ibuprofen and diclofenac where there was meaningful exposure. It is also important to note that there was a large spread of exposure through this meta-analysis, with some studies and comparators only having exposure to 12 weeks, while some doses of Vioxx and some comparators had exposure all the way out to 52 weeks.

[Slide]

This slide breaks down the number of patients enrolled for each dose and comparator, and the duration for which there is some data available. As you can see, the majority of exposure for Vioxx was at the two currently approved chronic doses, with a much smaller database at the dose used in the VIGOR trial. Again, the duration was much longer at these lower dosages compared to the higher dose for studies in the original NDA.

Ibuprofen, similar exposure in terms of numbers enrolled to Vioxx, 50 mg and, again, a fairly short-term exposure. Diclofenac did have a slightly larger number of patients enrolled in studies IIb and III and had a longer-term exposure. This asterisk applies also to the next slide. The only data points plotted are those for which there were 200 patients present at the end of the interval.

[Slide]

One caveat in looking at this is that confidence intervals are not here. If they were, there would be huge overlap because the number of events in this database was quite small. But, when trying to analyze a meta-analysis, we think it is important to look at the data that is there before combining to see how appropriate it is to combine and what trends are being enhanced and what trends are being diminished by combining studies.

This line, here, represents the ibuprofen group.

Exposure only extends out to 12 weeks for 200 or more patients, and this is the cumulative PUB rate. As you can see, this has the highest of all of the comparators across these studies. The Vioxx 50 mg is shown here. Again, exposure of 200 patients or more ends at 12 weeks in that database. The other three comparators, the Vioxx 12.5 mg, 25 mg, as well as the diclofenac are all shown here. They all three do have more significant exposure in terms of duration, and there is overlap with diclofenac between the two doses and only towards the end, again, these three data points can probably be looked at as overlapping as, in fact, with the confidence interval one may see across the entire table.

[Slide]

Conclusion of the review of the meta-analysis of Phase IIb/III studies, the Vioxx dose and duration of exposure do affect the associated rates. The ibuprofen and diclofenac did not perform similarly in that database. NSAIDs as a composite comparator may not be appropriate and, in a general sense, meta-analyses combining heterogeneous groups may be problematic.

[Slide]

Overall conclusions, Vioxx 50 mg was associated with a lower rate of PUBs and complicated PUBs compared to naproxen 1000 mg in patients with rheumatoid arthritis not requiring low dose aspirin. Risk reduction did extend across all high risk groups.

[Slide]

High risk groups, specifically the elderly and those with a history of prior PUB continue to have significant absolute risk of PUBs that was seen in this range for accrued rate. The generalizability of risk reduction to patients requiring low dose aspirin has not been evaluated. Generalizability to other NSAIDs, all traditional NSAIDs, remains a question. Thank you.

Cardiovascular Review

DR. TARGUM: Good morning.

[Slide]

I am Dr. Shari Targum. I am a cardiologist and medical officer in the Division of Cardiorenal Drug Products, and I am here this morning to present the cardiovascular safety data from the VIGOR study.

[Slide]

You have already heard some of this. I will briefly summarize the key features in the VIGOR trial. It was a large, comparative study with a nine-month median follow-up. There was no placebo arm, and the primary endpoint was GI in nature.

[Slide]

In terms of baseline demographics for this study population, it was mostly female, mostly under 65. A majority were Caucasian, and about half had any cardiac risk factor.

[Slide]

It should be noted that the two groups were evenly matched for hypertension, diabetes, current smokers, hypercholesterolemia and past atherosclerotic disease, which was less than 6 percent. We have no information on inflammatory markers, as was already mentioned.

[Slide]

Exclusions from VIGOR -- patients were excluded if they had angina or congestive heart failure with symptoms that occur at rest or minimal activity. If they had uncontrolled hypertension, and here it was defined; stroke or transient ischemic attack within the previous two years.

[Slide]

Other exclusions from VIGOR included patients taking aspirin, even low dose aspirin, or other anti-platelet agents, and patients requiring warfarin or heparin.

[Slide]

There was a note that patients with a history of myocardial infarctions or coronary arterial bypass grafting more than one year prior to study might participate if they did not require any of the excluded concomitant medications.

[Slide]

I would like to talk a little about the vascular events adjudication committee. This was a blinded, external vascular event committee comprised of three separate sub-specialty committees for cardiac, cerebrovascular and peripheral vascular events respectively, and there existed prespecified criteria for defining vascular events such as MI, etc.

[Slide]

This is taken from the procedures for adjudication. It is worth noting that the vascular events of primary interest for analysis -- these were prospectively defined events as opposed to the APTC endpoints, which have been discussed, which were post hoc. So, it is worth mentioning that.

The vascular events for analysis were split into primary interest and secondary interest. The ones of primary interest included myocardial infarction, unstable angina, ischemic stroke, acute arterial thromboembolism and sudden death or resuscitated cardiac arrest.

[Slide]

There were also noted vascular events of secondary interest, including pulmonary embolism, venous thrombosis, non-fatal cardiac thrombosis and transient ischemic attack. According to the sponsor, the definition of confirmed thrombotic events is a composite of these vascular events of primary and secondary interest.

[Slide]

This slide is a time-to-event plot. On the Y axis is cumulative incidence and on the X axis is months of follow-up. The events that I previously defined for you are here. The top curve is rofecoxib; the bottom curve is naproxen. You can see that the two groups are different. In fact, they are significantly different.

[Slide]

Points to consider -- there are no prospective randomized, placebo-controlled trials to support a cardiovascular benefit for naproxen. In addition, it is not known that rofecoxib is worse than placebo

[Slide]

In conclusion, regardless of mechanism, with cardiovascular benefit with naproxen or cardiovascular risk with rofecoxib, the cardiovascular data favor naproxen. Thank you.

Statistical Review

DR. LI: Good morning.

[Slide]

My name is Qian Li, a statistical reviewer from the Office of Biostatistics. I am going to discuss the meta-analysis for cardiovascular risk assessment for rofecoxib.

[Slide]

To begin with, let's first look at the cumulative incidence curves of thrombotic cardiovascular events observed in the VIGOR trial for rofecoxib 50 mg and naproxen. You have seen this curve before in Dr. Targum's presentation. The difference for cardiovascular events between the two treatment groups was statistically significant. Rofecoxib 50 mg actually doubled the risk of a thrombotic cardiovascular event in naproxen. Notice that the two curves start to diverge at six weeks after the treatment, and are further separated after the treatment. This suggests that the risk ratio is not constant over time.

[Slide]

To further understand the risk of cardiovascular events associated with rofecoxib 50 mg, the sponsor conducted a meta-analysis which consisted of 25 studies and more than 28,000 patients. The key features of the meta-analysis are that different dose levels of rofecoxib were put together, from 12.5 mg to 50 mg. Studies of different durations were put together, with a duration from six weeks to more than one year. And, the different indications were put together by stratified analysis. Those indications include rheumatoid arthritis, osteoarthritis and Alzheimer's and back pain.

[Slide]

The issues we have about the meta-analysis focus on rofecoxib 50 mg. The question we have is whether the meta-analysis can adequately address the role of rofecoxib 50 mg in relation to cardiovascular events.

[Slide]

Let's first look at the meta-analysis data sets. Of the 28,000 patients in the meta-analysis data sets, there are about 6000 patients on rofecoxib 50 mg. Of the 6000 rofecoxib 50 mg patients, 4,047 patients were from the VIGOR trial, which is a long-term study, more than six months. Also, in the VIGOR trial there were about 1900 patients on rofecoxib 50 mg and about half of those 1900 patients are from a study that has a duration longer than six months. As you can see, there are not many patients in rofecoxib 50 mg outside VIGOR in this meta-analysis data set, especially for study duration longer than six months.

[Slide]

In addition, we have some concerns about the meta-analysis. One, the risk ratio between rofecoxib and the comparator may not be constant over time. This was observed in the VIGOR trial and the treatment difference started to show around six weeks after the treatment. So, a short-term study may not be able to demonstrate the treatment difference. We need long-term exposure data with a sufficient number of patients.

[Slide]

Another concern is that the risk may not be the same for different dose levels of rofecoxib. It is common sense that pooling may obscure the risk associated with the high dose group. This is not a conceptual concern.

[Slide]

In fact, there are data to suggest a trend of increased risk with rofecoxib 50 mg. This data, shown in this slide, was provided by the sponsor on request of the agency for studies with a duration of at least six months or longer. As you can see, 50 mg appears to have a higher relative risk ratio in comparison to both naproxen and other NSAIDs, including ibuprofen and diclofenac. This slide is not to show that there is a dose response, but not to deny the higher risk of 50 mg rofecoxib.

[Slide]

To summarize the major limitation, pooling different dose levels is problematic for evaluation of rofecoxib 50 mg. This makes the meta-analysis invalid to assess the risk of rofecoxib 50 mg. Furthermore, there is not enough data in the meta-analysis data sets that has rofecoxib 50 mg outside the VIGOR trial, especially for a duration longer than six months.

[Slide]

In conclusion, the meta-analysis doesn't resolve the role of rofecoxib 50 mg in relation to the risk of cardiovascular events observed in the VIGOR trial. Thank you.

Summary

DR. VILLALBA: In the second part of my presentation I want to go over several important issues.

[Slide]

I will cover the general safety in the VIGOR study, then talk about cardiovascular safety. Actually, this is not the last set of slides I have because I have changed the title of this subsection and I will explain why later. Then I will talk about risk/benefit assessment and co-use of aspirin, postmarketing safety and the conclusions.

[Slide]

Evaluation of general safety in the VIGOR study was done by looking at routine safety parameters, such as death, serious clinical adverse events, dropouts, lab adverse events. These were prespecified in the protocol, and we requested that an additional analysis of number of hospitalizations. There were also prespecified analyses of NSAID-related events that I mentioned earlier.

[Slide]

This is the table of deaths in the VIGOR study. As you can see, the number was small and it was similar in percentage, a little higher in the rofecoxib group but too small to make any meaningful statistical comparisons. The most common cause of death was cardiovascular in both groups, and I just want to point out two cases of death related to GI bleeding in the rofecoxib group and one case in the naproxen group. Regarding the patient with hepatic necrosis on naproxen, this happened after the end of the treatment but it could have happened during treatment. But the important issue is that this patient was concomitant methotrexate, therefore, this cannot be attributed only to naproxen.

[Slide]

I will go through slides with the safety endpoints, and I don't want to spend too much time on each slide. The general point that I want to make is that GI safety favored rofecoxib clearly and consistently. However, the overall safety was in favor of naproxen. There was an equal number of events, all higher in the rofecoxib group as compared to the naproxen group. Here we have serious adverse events with an incidence of more than one percent.

[Slide]

Here we have dropouts due to adverse events. Again, the number is similar but if you go by category the number of cardiovascular events specifically is higher in rofecoxib than in naproxen, and that makes the total number similar.

[Slide]

This is the number of hospitalizations, which is consistent with the serious events. We thought this group would give us a more clear idea of how many patients really required nospitalization.

[Slide]

Regarding laboratory adverse events, the number was higher in rofecoxib as compared to naproxen. There were 22 dropouts due to laboratory AEs in the rofecoxib group as compared to 12 on naproxen. There were three serious hematologic events, leucopenia and one case of aplastic anemia in a patient who died of pneumonia complicating aplastic anemia. The three patients were on methotrexate.

[Slide]

This is the list of prespecified NSAID-related adverse events and CHF. The sponsor has already shown this slide but not with the p values. Actually, the p values are kind of irrelevant in that when we look at safety we don't look for statistical significance differences; we look for trends. But, in any case, for GI and for hypertension there was a statistically significant difference in favor of rofecoxib. Then, we have edema-related, liver-related with trends in favor of naproxen, and for renal there was a similar number of dropouts.

[Slide]

In summary, the GI safety favored rofecoxib but overall the general safety parameters trended in favor of naproxen, particularly due to the excess in serious cardiovascular events in the rofecoxib group.

[Slide]

I am going to talk now about cardiovascular safety and, as I mentioned, I changed this part because I had included several slides about studies using aspirin in cardiovascular prophylactic trials and then I decided to take them out because there are many cardiologists here that I hope will address that issue.

[Slide]

This is the time-to-event plot again. I apologize because it doesn't read very well but that was the table provided by the sponsor and we cut and pasted from the submission to make this slide. But I want to make several points here. I know it was shown by two reviewers earlier. On the Y axis we have the cumulative incidence of events and on the X axis we have the follow-up in months. What is very important here is the number of patients at each time point. You cannot read it well but there are 4000 patients per arm at the beginning, approximately 3000 patients at 8 months, and then the curve is cut when there were 500 patients approximately in each arm.

As we mentioned before, the separation starts at six weeks and is maximal after eight months, and we don't know what happened after ten months. This trial was appropriate with a long follow-up for looking at GI events, but probably not long enough for looking at cardiovascular events. Here, as you can see, the relative risk of developing serious cardiovascular events in VIGOR was 2.37, so a little more than twice.

[Slide]

Here I included the definitions, and you were already primed to these definitions so I don't need to spend too much time on that but they were really confusing to me when I did the review. So, I thought it was nice to put a slide together. The endpoints that the study used, the predefined endpoints were the adjudicated, confirmed serious cardiovascular events, confirmed by the case review committees. This was prespecified in a standard operations procedure that had been written long before the VIGOR trial was even started because it was planned to be used in all trials of rofecoxib. But this was really after the Phase IIb/III trials were completed.

The APTC is the composite endpoints of cardiac death, non-fatal MI and stroke, and this includes hemorrhagic stroke and excludes peripheral events, and also excludes unstable angina and TIAs.

[Slide]

Here is the list of events that were included for analysis.

[Slide]

This is just to show you how the same events can be seen in different ways if you look at the investigator reported events, adjudicated events or APTC composite endpoints. In any case, there is consistency and rofecoxib has the higher risk, almost twice or more than twice in the three ways of looking at these events. But, as you can see, the number of events with the APTC composite is smaller than looking in the other ways. In any case, this is the way it was prespecified. The APTC was post hoc but it is a way that is widely accepted in anti-platelet trials, and I think that understanding this difference will allow us to try to compare this with other published data that I hope some cardiologists will discuss.

[Slide]

This is the data. Now, what are the hypotheses? One hypothesis is that this is the prothrombotic effect of rofecoxib, and we do have the biological plausibility to backup this hypothesis. If this is true, is this related to the 50 mg dose? Is it related to the exposure? Or, is it related to the disease? We don't know. Is this a cardioprotective effect of naproxen? The sponsor has put together a very strong argument in favor of this hypothesis and there is also biological plausibility to explain that. But, it could be that none of these are the factors, that there is some other unknown factor. So, I just want to point out that if we are going to accept the cardioprotective effect of naproxen, this is a very impressive cardioprotective effect.

We have a median follow-up of nine months in a population with no medical indication for cardiovascular prophylaxis in a relatively small size because all the cardiovascular preventive trials include large numbers of patients followed for several years. Therefore, it is not very convincing to us that this is the whole explanation, and there are no controlled studies of naproxen versus placebo for cardiovascular prophylaxis. There are some available placebo-controlled studies with aspirin and I would really challenge the cardiologists here to explain to me how this correlates with what we know from those data.

[Slide]

The sponsor performed a meta-analysis with 28,000 patients to try to demonstrate that there was no evidence of prothrombotic effect in the whole database for rofecoxib, however, there are important limitations to that meta-analysis and, as Dr. Li already discussed, the studies were of different lengths, from 4 weeks to 86 weeks, and most patients were exposed for less than 6 months. You remember from the time-to-event curve, before 6 months you are not going to see much. Therefore, we would like to see what happened after 6 months or even after a year.

the study also included different doses, 12.5, 25 and 50, and most patients were exposed to the 25 mg dose or less. There were multiple comparators which may be associated with different risks of cardiovascular events, and there were different diseases that may be associated with different risks of cardiovascular events.

[Slide]

Out of the 28,000 patients only 600 -- and I think that this number is different from what Dr. Li presented but, anyway, less than 1000 patients were exposed to 50 mg a day for at least 6 months in studies other than VIGOR. So, I don't think that this meta-analysis can answer the question raised in a randomized, controlled study, large study with one dose with a 9-month follow-up.

[Slide]

In summary, regarding cardiovascular safety the VIGOR study favored naproxen. In cardiovascular thrombotic events for hypertension, CHF or hypertension, fluid retention and edema we had a signal in the NDA and this is dose dependent. However, for cardiovascular events we don't have a good explanation. The original NDA had a small database. The sponsor's meta-analysis has serious methodological limitations to answer the question.

I did not include in the slide the Alzheimer's studies, and I have not reviewed those studies, but the number of patients included in those studies was less than 1000 patients per arm, the two of them together. Therefore, these studies were not powered to show any difference with placebo. I will not make any conclusions about those placebo studies in Alzheimer's disease. Also, the dose that was used in that study was 25 mg, not 50 mg.

[Slide]

Now, regarding risk-benefit assessment and co-use with aspirin, we know that a large part of the patients with arthritis will probably qualify for cardiovascular prophylaxis. Patients with increased risk of certain cardiovascular thrombotic events should be on concomitant aspirin. However, the effect of concomitant use of rofecoxib with low dose aspirin on GI and cardiovascular risk is unknown. The sponsor had conducted, I think, five studies that allowed aspirin from the start. Three of those five studies were study 85, 90 and 58. These studies were 6-week studies and looked at the 12.5 mg dose. Therefore, those cannot really address the issue.

And, there was a rheumatoid arthritis study that I didn't have the opportunity to review, and I think this is in one of the Phase III studies for efficacy in rheumatoid arthritis, and the only one that had a large number, although it was kind of short for what we are looking for, was study 102, the ADVANTAGE study. This was a 5500 patient database to look at rofecoxib 25 mg versus naproxen 1000 mg a day, and this population was allowed to use aspirin and approximately 12 percent was using low dose aspirin.

These are the results. This is just preliminary data. So, I don't want to make any interpretation. But, you see that the events seem to go in the same direction. Again, this is 25 mg and it is only 12 weeks, and it was a different population because these were patients with osteoarthritis.

[Slide]

In summary, there is not much data on concomitant use of aspirin.

[Slide]

Regarding postmarketing, I have one slide just to mention that we have received reports of NSAID-related events -- GI, renal, liver, anaphylactoid reactions, prothrombin time prolongation with coumadin co-use. So, the safety profile looks like other NSAIDs. And we have received reports of serious GI events and even deaths in postmarketing.

[Slide]

In conclusion, successfully VIGOR showed that rofecoxib was superior to naproxen, and only naproxen, not other NSAIDs, in a population of patients not taking aspirin. Overall, there was no safety superiority of rofecoxib over naproxen, mainly due to an excess of serious cardiovascular events in the rofecoxib group compared to the naproxen group. Rofecoxib 50 mg is not the dose approved for chronic use; 12.5 and 25 are the doses approved for chronic use. Although 50 mg is approved for treatment of acute pain, the chronic use of this dose is not recommended.

[Slide]

Postmarketing safety raises the issue that serious GI events are still present, particularly in high risk populations. And, we ended with important questions. Is there a prothrombotic effect of rofecoxib? And, what would be the impact of chronic co-use of low dose aspirin in GI and cardiovascular events? That is my last slide.

DR. HARRIS: Thank you, Dr. Villalba. I am going to ask members of the committee if there are any questions they have related just to clarification of any of the data that was presented by the FDA. I will go left to right this time. Yes?

DR. WOFSY: Thank you. Two of the presentations, Dr. Villalba and Dr. Goldkind, commented on serious GI complications. Dr. Goldkind pointed out that in high risk patients there are serious GI complications that occur in patients on rofecoxib, and, Dr. Villalba, you pointed out that in postmarketing there were serious GI complications. There are also serious GI events in people who don't take these drugs, and people who take penicillin, and people who take anything. Do you have any data to bring to bear on whether there is more of this than you would expect? What does it mean, in other words, that we see this? We see this in every conceivable population.

DR. GOLDKIND: Yes, I think what you are looking for is an absolute underlying risk of events, and there are databases that address that. I think yesterday there were some slides that spoke to that issue. The problem is comparing across databases is difficult. Just the time element, looking historically, at a database is difficult because the definitions used to define an event in one study may be hospitalization, in another it may be death, in another it may be a symptomatic ulcer. So, the definitions are different, and how well you ascertain those events changes over time. A patient with an ulcer now, even if they have an episode of hematemesis, may be endoscoped as an outpatient and if there is no high risk findings at endoscopy or where the doctor is confident there won't be rebleed, you may not even hospitalize. Whereas, in an earlier database that person would have been not only a PUB or a POB but would have been considered an even more serious event. So, I don't think there is a good answer to the question of how many of the events or what percentage of the events that we see in the rofecoxib group are related to underlying risk factors and, in fact, are not attributable to the drug.

DR. WOFSY: I take your answer I think to be as clear as it can be but, in effect, I am asking what point are you trying to make by giving us this information.

DR. GOLDKIND: In the high risk group or in general?

DR. WOFSY: Either. By giving us the information that in postmarketing experiences or in high risk patients GI events happen, what is the point?

DR. GOLDKIND: I think it is important to know. I mean, there are limitations of postmarketing data. If there are 13 million prescriptions, you know, you could have a list that would extend through the entire PDR if you were going to list anything ever reported. Actually, I will let Dr. Villalba respond to that since that was her point.

In terms of the issue of relative risk, I think it is very important. Again, you can look at the same data and say because of the advantage, the relative risk reduction, this is precisely the drug to use, or you can say the underlying -- the absolute risk, I should say, not the underlying is high enough -- how much is drug; how much is disease we don't know, but if it is high enough there then you reassess, in a sense I guess, the drug category or the whole treatment modality as NSAID versus another modality altogether. That, obviously, relates to the strength of the indication. As I said in my discussion, if you have strong indication for a category of drug and you need the pharmacodynamic properties, then you obviously choose that one that appears safer.

DR. VILLALBA: My answer would be that we have a label that has a GI warning for non-steroidals and, based on this study, the sponsor is proposing to downgrade that label and move it to the precautions section, and be different from the other NSAIDs, and I think that the fact that we still have reports in postmarketing of these kinds of events supports the fact that we shouldn't be changing -- well, I mean modifying the label, yes, but a dramatic change in the label, I think that is not warranted.

DR. HARRIS: Can I take the chair's prerogative and just ask a question myself, if I might? Is there a stage in the postmarketing surveillance where one says that we have seen something often enough that, you know, there is an alert? I mean, there are alerts and, you know, can one get a sense of that her?

DR. VILLALBA: I am glad that the reviewer from postmarketing is here, so could someone answer that question?

DR. BRINKER: Hi. My name is Allen Brinker and I am a medical epidemiologist and one of a group of people from postmarketing that helps review these drugs. As far as your question goes, there is no threshold for an absolute signal. The safety evaluators and the medical officers that are involved with this drug all review these case reports, these spontaneous case reports that bubble up from an unknown number of patients that are exposed to these drugs. It doesn't take very many cases of fulminant liver failure in otherwise healthy people for us to get very interested in drug safety. If we see a lower threshold of events, GI events or cardiovascular events that float up from a population at risk, it is much harder to make a signal out of that. Does that help you?

DR. HARRIS: Yes, I think it does. Dr. Wolfe, you had your hand up first so I am going to give you a chance.

DR. WOLFE: I want to actually address this issue because the question was asked is there a background prevalence of GI bleeding and the answer is yes. I think that has to be very carefully considered when you talk about a post hoc analysis because a person who has, for example, *H. pylori* infection and has a bleed, if they are taking NSAIDs who knows what caused the bleed in that situation. I don't think any claims were made here by anybody that you are decreasing the risk to zero. There is still going to be a background level and, actually, the older one gets, as we have seen, the higher the prevalence rate.

DR. PINA: A question for Dr. Villalba. In study 102 I noted that the slide that you showed had ischemic CVAs of six versus zero against naproxen. Aspirin was allowed in the trial. Were any of those patients, indeed, on or off aspirin? Do we know that?

DR. VILLALBA: Actually, this is just preliminary data. I have not reviewed this study. A complete report has not been submitted to the agency and these preliminary data were submitted because we requested it. This is the last database. We want to know what is going on. But the sponsor could answer that question.

DR. HARRIS: Please.

DR. REICIN: Can you hear me because the mike isn't on? The five strokes occurred in non-aspirin users.

DR. HARRIS: Dr. Cryer?

DR. CRYER: I would just like to follow up to Dr. Wolfe's response about this background rate that was seen in the postmarketing experience. I addressed the same question that you did with respect to the postmarketing experience on GI bleeds with rofecoxib. According to my assessment of what I read in our briefing documents, it appears that the rate of complications that have been experienced with rofecoxib are actually less than would have been expected given the background rate in individuals not on NSAIDs.

DR. HARRIS: There is just one other question I have to ask, and this is talking about bubbling to the surface. There seemed to be some comment in the postmarketing surveillance about early renal events. In fact, the thinking was that it occurred later but it seemed as if with, I think, both of the COX-2 inhibitors there were some of these events that were reported that occurred earlier than one might anticipate. Now, we are not sure whether it is the drug, not the drug, or something. Is this one of the things that perhaps might bubble to the surface?

DR. VILLALBA: I would ask again the reviewer from postmarketing, if you want to answer that question.

DR. BRINKER: Were you directing this comment towards postmarketing or towards our interpretation of the VIGOR trial?

DR. HARRIS: Postmarketing entirely, and this was again from reading some of the background data and I think there was a comment made about some renal events occurring early after taking these drugs and apparently the labeling indicated otherwise.

DR. BRINKER: Indeed, we have data on that. Getting back to what spontaneous reports data are all about, and they are really designed for the qualitative detection of a serious, rare and unexpected event. We can present data from these case reports that we have received on this issue if you want a qualitative description of some of these cases that have come in.

I will also take this question back to the people who have looked at the VIGOR trial and see if they want to comment on anything that they saw in the setting for a quantitative description of risk in a randomized, controlled trial.

DR. VILLALBA: As I mentioned regarding renal events, there was no difference in dropouts due to renal-related events as per the sponsor numbers. There were more renal events in the rofecoxib group but there was not a large difference between the two of them.

DR. HARRIS: Thank you. Dr. Nissen?

DR. NISSEN: Several reviewers commented on this apparent inflection point in the cardiovascular event data from eight months on. I wonder about how much confidence the reviewers have that that is a real phenomenon as opposed to just sort of an anomaly of the statistics of all of this. Is it consistent across groups? Was it seen, for example, in the Phase IIb/III data from the sponsor? What do we know about this? Is that a real phenomenon? How certain are we of that?

DR. VILLALBA: Well, the Phase IIb/III was a smaller database and the doses were all kind of doses, and the number of patients exposed to any dose for more than six months was limited. Therefore, I don't think that we can compare the two databases but it may be related to the number of patients at that point. There were close to 1000 patients at eight months.

DR. HARRIS: I think you are referring to that apparent sharp increase after eight months, and I am pretty sure the sponsor gave a response to that, and I would like you to repeat it.

DR. ZEGER: Hello. I am Scott Zeger. I am a professor of biostatistics at Johns Hopkins University, and I had a chance to review these data and also noticed that inflection point and thought some about it. I asked Merck to do some investigations about it, and there is no statistical significance to that inflection point based upon their looking for a change in the relative risk over time.

But I also got the data myself and did some analyses, and I cut it as many ways as I knew how and there is really no evidence that there is a meaningful change there. In fact, if you just think about it for a second and take the last 20 events, which is from month 9 on, and there is a relative risk of about 2.3 over the whole period of time, and you say how should the 20 events split, and they should split with a 2.3 relative risk of about 14 to 6 --

that is how they should split if there is no change. What we saw was 16 to 4. So, it was 2 events difference than what you would expect overall.

I noticed the shape as well and I looked into it quite carefully, and there is really no evidence -- no statistical evidence to lead us to conclude that there has been a change there.

DR. NISSEN: That answers my question.

DR. HARRIS: Dr. Pina?

DR. PINA: I am trying to get a handle on the thrombotic rate in the patients in VIGOR. Dr. Targum, you did an assessment. In your evaluation of the packet that we have you have a table of patients who perhaps should have been on aspirin because they had significant risk factors for thrombotic events and patients that did not. It was a little bit confusing to me. Can you clarify that? What was your understanding of separating the patients that way?

DR. TARGUM: I am at somewhat of a disadvantage by not having it in front of me, but what I was presenting was an analysis that the sponsor had done which I, frankly, thought had limitations. I thought it was slicing the data -- I thought we had it so that I had something to refer to. When I looked at the safety update I noticed that the confidence intervals for both the aspirin indicated and aspirin not indicated subgroups still sere consistent and that they were against rofecoxib and favored naproxen, regardless of whether aspirin was indicated or aspirin was not indicated. So, my feeling is that, regardless of whether you take that post hoc subgroup or not, the trend was against rofecoxib.

DR. PINA: Thank you for the clarification.

DR. VILLALBA: This is from my briefing document and this is the data that you are referring to, and it shows that for that subset of patients, retrospectively identified as candidates for secondary prevention, the risk was five times higher for rofecoxib. For those who were not at risk, who were the majority, the risk was still twice.

DR. REICIN: Can I show one slide, slide 1449?

[Slide]

You are correct, the risk was reduced in the naproxen group whether patients had "an indication" for aspirin or not. Early on, before we did the safety update report, most of the risk was in the aspirin indicated group. With the safety update report it was more evenly distributed.

[Slide]

One thing that struck me in reviewing the data -- this is in the APCT endpoint in those for whom aspiring therapy was indicated -- if you go over to the naproxen group you can see that these are patients who had a prior

MI, prior angioplasty, CABG, and there were no myocardial infarctions in that group and that was one of the things that was surprising to us.

DR. HARRIS: Thank you. Okay?

DR. LIM: I am Stan Lim, FDA statistician. I just want to get back to the issue about the inflection point and whether that is real or not. I don't think you can really answer that question based on statistics but I would point out that VIGOR is a rigorously defined, long-term trial and we see what we see. Now, Dr. Li also presented some data. I mean, granted it is not something that we had realized in depth, but we took data from the sponsor and put it in table form to compare rofecoxib 50 mg versus naproxen versus diclofenac and ibuprofen. If you remember that slide, it says that if you look at data that are six months or longer, there appears an increased risk.

DR. ZEGER: I just wanted to make the point that I was not saying this proves that there is no change. I was just trying to be responsive to the question. Is there strong evidence in the data of a change, and my answer to that is no.

DR. HARRIS: Thank you. Dr. Harrell?

DR. HARRELL: On that point, I think if today and yesterday we never saw a single point estimate or a single p value or a single power calculation but only saw confidence intervals we would be so much better off than we are right now. But on this particular graph what we need to see is a confidence band for the hazards ratio over time. It is a real easy graph to make and I hope somebody has made it.

DR. HARRIS: Thank you.

DR. SAMPSON: Dr. Goldkind, I was wondering -- I know it is dangerous to compare across studies and populations, and maybe you can correct me, the complicated PUBs today I should think of as the POBs of yesterday. Is that correct?

[Laughter]

DR. GOLDKIND: It is dangerous to cross compare. Again, there would be confidence intervals around each definition. Actually, if sponsors from yesterday or today want to make comment after I do, that would be fine. I think that the PUB today would be, in a rough sense, the complicated -- the POB, I am sorry, the complicated POB would be closer to the complicated ulcer. The PUB which included symptomatic ulcers would be the composite endpoint that was looked at yesterday, although, again, there were some definitions -- how close they would be if you kind of used the definitions from one to the other, I am not sure.

DR. SAMPSON: To follow up on this, and again I recognize that yesterday's study was done in a mixed population of RA and OA, but there is something that you folks pointed out yesterday -- and, again, please correct me because I am looking at sketchy notes here -- yesterday you pointed out that the Celebrex PUB rates continued to rise after six months, while diclofenac and ibuprofen seemed to flatten out. Today we see the Vioxx rates rising after six months and the naproxen rates also rising after six months. I was wondering if you would have any comment about why biopharmaceutically the naproxen rates would continue to rise while the diclofenac and ibuprofen remained somewhat flat.

DR. GOLDKIND: Actually, the pattern seen yesterday for the composite of symptomatic and complicated, which would be the equivalent of the PUB, again a lot of confidence intervals and all the qualifications of cross comparing, but yesterday that composite actually did show that events continued to accrue in all three groups looking, in general pattern, similar to what was seen here. So, the question would be complicated ulcers appear to manifest themselves earlier in the NSAID comparators in the CLASS study, whereas in this database that wasn't seen, and I don't have any answer for why the complicated ulcers -- you know, there are a lot of possibilities.

DR. SAMPSON: You wouldn't want to ascribe it to study basis versus drug basis? Hard to say?

DR. GOLDKIND: It is hard to say because there are issues of informative censoring. Yesterday the sponsor alluded to whether that would have played a role. What I think we have learned in these large, simple trials is they may be large but they are not simple and there are so many factors that would play into why you may see change over time -- it is too complicated, I think, for me to venture an intelligent answer.

DR. HARRIS: Thank you.

[Slide]

DR. VILLALBA: This shows the confidence interval for all patients randomized. The estimate is 237 and the 95 percent confidence interval is here and that is the p value.

DR. HARRELL: What I was talking about was the instantaneous hazard rate at a given time estimated for a lot of different times with confidence interval on it.

DR. ZEGER: This is Scott Zeger again. Just in response, what I actually did was exactly what you are saying. I estimated a relative rate within each of two-month intervals and I can give you that after lunch.

DR. HARRELL: Just to be nit-picky, Scott, I don't want it in two-month intervals but I want it as continuous, you know, smoother --

DR. ZEGER: Right, that would be even better and I can't give that to you after lunch.

DR. HARRIS: Thank you. I think we must push on.

We are moving now to our open public hearing, and Dr. Sidney Wolfe, Director of Public Citizen Health Research Group, has a statement.

Open Public Hearing

DR. WOLFE: I just want to talk about three things, one, the GI toxicity or reduction in it; two, the cardiovascular problems; and just an overview on how we got into this mess that we are in right now.

There are three ways in which the group in the VIGOR study differs not only from the general population but from a lot of other things. One, it was just rheumatoid arthritis and, given that the drug isn't even approved for that, the typical user of Vioxx can hardly be construed as someone with rheumatoid arthritis.

Secondly, the percentage of people -- 56 percent of the people in the study were takings steroids for their rheumatoid arthritis. This is almost twice as high as the percentage taking steroids in the CLASS study.

Third, a comparator drug was used which clearly is not one of the two safest drugs. A chart that I distributed yesterday is a review of all the case control studies on all the NSAIDs. In six of the seven comparisons ibuprofen turned out to be safer than naproxen. It was tied in the seventh. In five of the seven comparisons diclofenac turned out to be safer. Those two drugs were, therefore, I think appropriate comparators for the CLASS study. They would have been appropriate comparators for this. So, a more dangerous comparator drug is always going to make a drug, such as Vioxx, look better.

If one does a subgroup analysis, which the FDA did, very clearly on the issue of the steroids, people taking steroids who were then given naproxen had a much bigger increase in the amount of ulcers than occurred in the group that were getting Vioxx, such that when you looked t the people who didn't take steroids in the study there was not a statistically significant reduction in GI events in the people taking Vioxx who were not taking steroids compared with Naprosyn.

So, there are several things that I think cloud up validity of the results on the GI toxicity, and I would argue that if you had taken Celebrex and put it in this kind of study you would have gotten probably very similar results as far as GI toxicity.

As I mentioned yesterday, from what I again described as an exciting paper in the proceedings of the National Academy of Science, and probably a dozen or so other papers in the literature, clearly in the role of healing tissue, including ulcers in this case or any GI tract abnormalities, cyclooxygenase-2 is very important and, therefore, it is not terribly surprising that you really don't do a better job than you would expect from the not representative GI endoscopy studies in getting rid of these ulcers compared to other drugs.

As far as the cardiovascular toxicity, someone mentioned some of the other studies in which people were getting aspirin. Yes, there is not a statistically significant increase in MIs but if you combine the two studies, I guess 090 and 085, a total between the two of maybe 800 or so patients in each group for Vioxx and nabumetone, there are four MIs in the group getting Vioxx and only one in the other -- not statistically significant; small numbers and, as was pointed out, short duration but still a suggestion. There are also suggestions from the CLASS study, although again not reaching statistical significance, of an excess of MIs in people getting Celebrex.

So, in conclusion of these two points, I would argue that there really isn't any credible evidence of a difference between these two drugs in either their GI toxicity or so-called reduction of serious GI complications, or in their propensity to be associated with a larger number of cardiovascular events, including MIs. I think that the two possibilities, or three, the three being "other" to explain this difference, (a) being the anti-platelet activity that is not present in these drugs and, (b) being prothrombotic activity -- my guess is that when we know much more than we do now both of them will be in place, but I certainly agree that one can hardly explain the results of the five-fold increase in heart attack risk, statistically significant, in the VIGOR study by simply the fact that it lacked the anti-platelet activity of Naprosyn. I mean, what I could see of that case-control study which is a case-control study with all of the flaws inherent in case-control studies compared with a randomized, controlled trial, the risk ratio was 0.6. That is very different from a five-fold increase in heart attacks.

Finally, I would like to say that the FDA has done an extraordinarily good job in reviewing and presenting this massive amount of data, such that the next time one of these drugs comes along I think these studies should be required before approval. There is no reason why studies lasting six, eight, nine months on an important safety issue should not be required for drugs that don't arguably have any safety advantage over other drugs. There is absolutely nothing in the evidence prior to approval to suggest that these drugs, from an efficacy standpoint, were a breakthrough and there certainly should have applied long ago to other drugs but we now know more than we did. I think particularly the increased risk of cardiovascular problems behooves the FDA to require safety drugs. We are not talking about ten-year studies; we are talking about studies that are six, eight, ten months, that should be done.

I believe that a massive fraud has been perpetrated on people in this country who have spent billions of dollars on drugs that are not arguably any better, to the extent that Celebrex didn't even make the grade in terms of its pain relief. It was not approved initially for that. And, we have not yet seen the data that would justify approving Vioxx for rheumatoid arthritis. To sell a song based on some interesting, but in the larger picture I don't think that relevant GI problems that are somewhat relieved, is really to mislead people. I think that the emphasis has been in the presentation that I saw this morning on overall safety. The enzyme is present all over the body. It is going to have what turn out to be adverse effects in many other organs and tissues, which I suspect will come in studies in the next couple of years, and I just hope that everyone learns from this and the next time something like this occurs these studies will be done prior to approval instead of afterwards. Thank you. If you have any questions, I would be glad to answer them.

DR. HARRIS: Thank you very much, Dr. Wolfe. If there are no other comments from the public, I would like to move towards adjourning this session but before I do so, I am wondering if I can ask everybody, as precise as one can be, that we get back here at 1:15 p.m. We are running a little late and I am going to give you about 55 minutes for lunch. Thank you.

[Whereupon, at 12:20 p.m., the proceedings were recessed, to be reconvened at 1:15 p.m., this same day.]

A F T E R N O O N P R O C E E D I N G S

DR. HARRIS: I would like to call the afternoon session to order.

Discussion and Questions

Vioxx Questions

This afternoon we are going to consider the questions that have been posed to us by the FDA. I am going to start immediately with question one.

Please comment on the differences in cardiovascular event rates between the Vioxx 50 mg and naproxen groups. Are further studies warranted? Does this finding warrant consumer/prescribe awareness? If so, in what format?

So, there are several questions. I agreed, as we did yesterday, to start with our experts and we are going to start with our cardiovascular experts, and Dr. Steven Nissen would like to present some data.

DR. NISSEN: Thank you. First of all, I appreciate the opportunity to be here. Obviously, this is an issue that crosses several different disciplines and, as one of the two cardiologists here, I thought it would be appropriate if I helped the committee to think through what we have seen here in the cardiovascular data and maybe talk a little bit about what I think the implications are.

[Slide]

I think we are all aware of what the data shows but I want to reiterate it, particularly for three what I would call hard endpoints, cardiovascular death, myocardial infarction, stroke and the composite of those three. I took these data from the report. I don't have access to the database and I want to say right from the very beginning that I have neither shared this data with the agency or anyone else here. This is my own analysis of the data. Take it as you will and, obviously, I may not have exactly the numbers correctly but I certainly did my best.

So, the question then that comes up that I think has been in the back of all of our minds is whether or not what we are seeing here in these differences in events is a very low rate in the naproxen group or a very high rate of events in the rofecoxib group. It is a different question to answer, but I think there are some things that can be done that will help answer it.

I want to also point out just a couple of things here. At least in my analysis, the acute myocardial infarctions events are really driving a good deal of this. So, that is obviously an important aspect of this.

Well, how could we go about analyzing which of the two hypotheses makes more sense? Well, one way is to ask the question whether the naproxen event rates are similar to event rates in patients who receive aspirin with similar demographics, and also ask the question whether the rofecoxib event rates are similar to the event rates of patients who don't take aspirin, who are on placebo, in a similar risk category.

Let me say from the outset that I am well aware, as all of you are, of the limitations of this sort of statistical analysis, and I will not even suggest that it means more than, if you will, a reality check that may help us to understand the data a little bit better. This is not hard science and it is not necessarily, you know, good statistics.

[Slide]

In looking at this to try to, at least in my own mind, get to some comfort level, I was able to identify a study, recently published, that has demographics that are in the same ball park, and this is the primary prevention trial, or PPP -- Primary Prevention Project, published in Lancet really only a few weeks ago, which was an aspirin versus no aspirin trial in about 4500 low risk Italian individuals who had at least one cardiovascular risk factor. However, included in those risk factors was age greater than 65. So, if you were over 65 you were deemed to have a cardiovascular risk factor. They had no prior MI or stroke. The mean age was 64 years. There were more females than males, which again had some similarities to the database in the VIGOR trial. Fifteen percent were current smokers, which is amazing because anybody who has been to Italy --

[Laughter]

-- I can't imagine anybody could find an Italian population that only had a 15 percent tobacco use, and 68 percent had hypertension.

[Slide]

Is this a reasonable comparison? Well, as you would expect, there are differences. Compared to VIGOR this population is six years older. That is reflected here. More of them were over the age of 65. The female predominance is a little bit less. They had more hypertension. The VIGOR patients were a little bit more likely to be smokers, and the PPP patients were a little bit more likely to be diabetic.

Again, these are all limitations of comparing two different trials and, again, I really want to be cautionary about any analysis of this kind, but I think we have to do this if we are going to have any idea of whether any of this makes any sense or not.

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In the PPP trial there were statistically significant reductionism in events. That is, cardiovascular death, MI, stroke and the composite of the two. You can read the Lancet paper. I won't give you the confidence

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intervals and so on. I actually have a copy for anybody that would like to look at it.

Is it legitimate to compare the aspirin arm in the PPP trial to naproxen and the placebo arm to rofecoxib? I will let you be the judge of that. I am, however, aware of several things, that the comparison of two trials in different populations is inherently risk. The definitions of risk factors such as hypertension and diabetes are not necessarily uniform between these trials, and even the definitions of cardiovascular endpoints are not necessarily uniform. So, I would consider this analysis exploratory and, at very best, hypothesis generating but not more than that.

[Slide]

What did we see here? Well, it is a bit reassuring that the naproxen event rates in VIGOR and the aspirin event rates in PPP were very, very similar. If you do the confidence intervals here, these are really amazingly close. Cardiovascular death, MI, stroke and the composite in the VIGOR trial with naproxen and the aspirin arm of PPP were very similar. This, to me, provides some reassurance that what we may be seeing here, at least in part, is a protective effect of naproxen. If the event rates in the naproxen arm had been significantly different from the aspirin arm in PPP, I think the whole analysis would be much more different.

[Slide]

What about the rofecoxib versus no aspirin? Well, the cardiovascular death rate in the PPP trial was a little bit higher. The MI rate in the rofecoxib group compared to the no aspirin or placebo arm of PPP was higher. So was the stroke rate and so was the composite endpoint rate.

I think it is important to point out, what was not discussed here and I think should be discussed here, that I also looked at the MI rate in the CLASS trial with celecoxib and noted that these rates were quite similar in rofecoxib and in the CLASS trial. I think that is perhaps an important point for discussion.

[Slide]

What about the confidence intervals around these comparisons? If you assume that rofecoxib and no aspirin in PPP are the same, and look at the differences and then look at the 95 percent confidence intervals around the differences, this is what you see -- p value for death, not significant; p value for MI appears significant, and I use the word significant in quotes because these are two different trials. CVA, no difference, and a trend in the composite data towards significance.

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If I graph these, with no difference being this line, here, you will see that the confidence intervals for death cross this line. There is an excess of myocardial infarctions comparing rofecoxib to no aspirin. But stroke and the composite endpoint don't get to statistical significance.

So, again, within the limits of this type of analysis, there wasn't, in my view, except in the area of myocardial infarction, a very strong signal.

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What can we say then in conclusion? Well, the cardiovascular event rates for naproxen in VIGOR and for aspirin in PPP in relatively similar populations were low, and they were virtually identical. This would tend to support the hypothesis of a protective effect for naproxen. The event rates for rofecoxib are higher than the no aspirin arm of PPP, but there were pretty broad confidence intervals here, particularly when you consider that we are looking at two different populations.

Only the differences in MI rates are significant, but there were very few events. I would point out to everyone at the table that in the entire cohort there were only 24 myocardial infarctions, 20 in the rofecoxib group and four in the naproxen group. A shift of two or three MIs could easily have made a difference here in terms of the outcome with respect to this analysis. So, we are really talking about a very, very few events.

Accordingly, the possibility of higher event rates comparing rofecoxib to placebo can't be excluded but I think, on the basis of my analysis here, this certainly does not prove it. I think it is also important to note that there are essentially identical MI rates for celecoxib and for rofecoxib in VIGOR.

[Slide]

What do I think we ought to consider doing here? Well, I think the absence of a cardioprotective effect for both COX-2 inhibitors should be emphasized in the product literature. There is nothing I have heard either yesterday or today which suggests that either agent has a cardioprotective effect as do the non-selective agents, and I think that must be emphasized in the product literature.

I think we need further studies to investigate whether there is an excess of cardiovascular events in longer term exposure to both of these agents in comparison to placebo, and I think we need to know whether co-administration of aspirin can reestablish the cardioprotective effects of COX-1 inhibition without increasing the GI morbidity. I think those two questions have simply not been answered by any of the data that I have seen and I personally think we need a 2 X 2 kind of a factorial design study to be done where patients receive a

COX-2 inhibitor with or without aspirin and we try to find out what happens to event rates on both the GI side and the cardiovascular side when we do so.

I do think that these data suggest to me that at least some of the difference between rofecoxib and naproxen is due to naproxen benefit. I mean, that would be one conclusion that I feel reasonably comfortable with. Whether all of it can be attributed to that, I think you will have to make your own mind up about. Thank you.

DR. HARRIS: Thank you very much, Dr. Nissen. Can I make one comment again? I mean, this is merely data that is presented. It is very limited. There are obviously a number of reservations which you have mentioned. I want to reemphasize that. So, in terms of our deliberations, I really don't want it to rise to the level of other data that we have seen today.

DR. WILLIAMS: However, I think that what you summarized really summarizes my thinking with regard to what we have seen here, with one caveat, and I think that your first recommendation gives the implication that there is cardioprotective effect from the other NSAIDs and I don't think we have evidence for that effect, except what we have seen here on naproxen.

DR. NISSEN: Let me say I meant aspirin rather than other NSAIDs.

DR. HARRIS: Dr. Pina?

DR. PINA: I think Steve has also summarized my feelings about this, and my further concern and confusion relates again to this population which would have been a lower risk population to begin with. And, in this lower risk population -- even though when they went back and the FDA went back, there were patients who probably should have been on aspirin, that had some indications for being on aspirin, the population that will be using this will probably be the population with all the cardiovascular events. This is very similar to what we saw yesterday. In spite of that population being lower risk, I think that the rate of embolic events is still higher than what I would expect in this population.

I agree that probably naproxen is giving some anti-platelet effect and that accounts for some of the difference, but I don't think it accounts for the entire difference.

DR. HARRIS: Does anybody else on the committee want to comment on the differences?

DR. SAMPSON: Dr. Nissen, could you just comment for the non-physician on the difference in effect of a population having RA and the Italian population in terms of the events that you described?

DR. NISSEN: We just don't know, Allan. You know, I think that when you compare two different populations this is statistically very hazardous. That is why I was very careful to say that this is just exploratory. I think that we don't know what the native events rates are going to be in these populations. So, there is a lot that we just can't extrapolate from any analysis of this kind, and I really do want to emphasize what Nigel said as well, that, you know, I needed to do this just for my own kind of reality testing here because I needed to know were these event rates that we are seeing with rofecoxib -- were they way out of line with what we might expect in a population like this? I guess what I saw was they really weren't way out of line. They were maybe statistically greater but I think it is jut not proven yet to my satisfaction.

DR. HARRIS: Can I say something because there is a comment from the sponsor? I have to say that you mentioned two drugs here, and I am really torn right now because I think the representatives from Celebrex are not here -- but they are here but not in the line. So, I made a decision to allow you to make this statement. I think so far as the committee goes, I will accept comments but my own view is that I don't want to push it any further. That is why I say I don't want it raised to the level of the data that we have seen this morning. Nobody has had a chance to really examine this, and so I really don't want it to be overemphasized. Now, if there is a view about that on the committee, of course, I am prepared to hear otherwise.

DR. WILLIAMS: My comments were not based on his data. I thought what he presented summarized the way I feel about the other data that I have heard, that I think there has been good evidence that naproxen may have an effect on cardioprotection, and I think that we have not yet demonstrated that rofecoxib has a negative effect but there seems to be a trend in that direction and more study is needed.

DR. HARRIS: Oh, I have no problem with your comment. I think my problem is, you know, in terms of getting any other comment from sponsors or the FDA because we have not had a chance to look at this data and really it is just informal discussion here.

DR. PINA: I just want to go back to Dr. Sampson's question about rheumatoid arthritis. There is a certain number of patients, let's say, with long-standing rheumatoid arthritis who can have coronary arteritis and, therefore, can have myocardial infarction events based on the arteritis, but it is not the common presentation and it is usually long-standing disease in a much older population, pretty much severe disease. In most of the rheumatoid arthritis that we see in practice we don't see a lot of coronary events or they come to us with coronary events and we find out they have rheumatoid arthritis. I just wanted to follow up on the pathology.

DR. WILLIAMS: Just a comment, there is an increased risk of cardiovascular events in rheumatoid arthritis patients irrespective of vasculitis. Part of that is induced by the use of corticosteroids; part of it is induced by the chronic inflammatory state, and so forth. So, I would not say that it is only coronary vasculitis that would add the risk. There is a basic increased risk in cardiovascular events in rheumatoid arthritis.

DR. GUESS: Excuse me, I am Harry Guess, from Merck, and this is a perfect time -- we have looked at the literature on this and, actually, using the general practice research database we examined the risk of thromboembolic events in OA and in RA, adjusting for age and sex, and adjusting for other factors, and we have confirmed what Dr. Williams said exactly. It is about a 1.5-fold increase in RA versus OA. So, I feel, in our hands looking at it, it is consistent with what has been seen in the literature and there is an elevated risk in the RA population. Thank you.

DR. HARRIS: What I am going to do -- you have a comment? Sorry.

DR. CALLAHAN: I was just going to agree with Jim's comments. There is an increased risk.

DR. HARRIS: I want to pose the first question to the voting members of the committee, which is, are further studies warranted? Based on the data we have seen today, would you recommend that there be further studies? Are they warranted? Dr. Wolfe, maybe we could start with you.

DR. WOLFE: Actually, at this point, as was mentioned yesterday, we have to bring both of these together. We have to because there are two different studies which look at the impact and actually bring out the importance potentially of aspirin causing a lot of these problems. We can't say with certainty because of the statistical analysis. But, I would like to see some information with these studies on what happens if we do add aspirin to the mix for the people who were actually in need of taking aspirin -- to make this a real-life study. People who are elderly do need aspirin very commonly for cardiac prophylaxis. I would like to see what happens to the protective effects in the GI tract with aspirin.

Additionally, I think the FDA has to address the issue of the NSAID comparators. This has been brought up. You know, is there an advantage because we are looking at naproxen in this study comparing rofecoxib because naproxen has the higher toxicity? Or, was there a disadvantage at looking at ibuprofen? If there is some standardization we can compare apples with apples or Macintosh apples with certain types of oranges rather than different types of apples and different types of oranges. So, I think there has to be standardization before we can really compare these. The reality is whether we compare them or not, people in the community will compare these.

DR. HARRIS: Dr. Pina?

DR. PINA: I think we need more information and even this last point about rheumatoid arthritis -- I think that the rheumatologists probably see the patients with the more severe disease. They get referred to you and on our end, on the cardiac end we just don't see that many patients like that. So, it may be the patient population as I think is the case in this trial. It is a very different population. I think the database is rich and I think we have learned a lot from this database, very well presented, but it just elevates a whole series of questions again. What will be the use of this drug in the general population that will tend to have a lot of cardiovascular co-morbidities and will need aspirin?

So, would definitely say that, yes, further studies are warranted. Again, I compliment the sponsor on the richness of the data that they presented to us today.

DR. HARRIS: Dr. Nissen?

DR. NISSEN: I think, as I said earlier, I really do think it warrants further study, and I think that the two issues for me are do the COX-2 inhibitors -- does rofecoxib increase cardiovascular events over placebo? That is a question that I think we have to know. Secondly, can we neutralize that effect by giving a low dose aspirin, but at what cost in GI toxicity?

Those two questions, I do think, are still open questions that the data doesn't allow us to answer currently, and I think for the clinicians who treat both heart disease patients and patients at risk of heart disease, and people who treat patients that have arthritic disorders, those questions simply have to be answered.

MS. MCBRAIR: I keep looking at this from the viewpoint of the patient and what kind of knowledge theoretical patient is going to have when they walk in the doctor's office as to what they would like to have happen for themselves, as well as what the physicians are going to need to know in order to make the best decisions possible to prescribe the medications that may help the patient live with arthritis, as well as not have too many adverse effects along the way.

I guess I really do feel that there needs to be more study in this area, and I am struck both days with the lack of standardization of the two studies, the lack of standardization of what side effects are, what untoward effects are when we are trying to make these judgments, and the lack of standardization of how we compare these two drugs, how we would look at the whole picture. So, I just would encourage a lot more study here and us really taking time to think through what has been done and how to best proceed from here.

DR. WOFSY: I certainly agree that further studies are warranted specifically in this area, but I also want to make the point that further studies are always warranted. It is hard to imagine any presentation to this committee that wouldn't raise important questions. So, I think in focusing on the need for further studies it is also important to keep in mind that we have now seen in this meeting over the two days two large, well constructed, carefully done studies that address the important questions, and there is important information in these studies as well as unanswered questions. I recognize that that would be an important part of what we do this afternoon and I just want to reemphasize by saying that, of course, further study is indicated but my own view is that there is information here that is important to share with the public and with people who prescribe these medications, and there are important things learned from these studies, as well as questions raised.

DR. CALLAHAN: I agree with what has been said today. I do think there is a need for further studies, but I would like to reiterate the point that was just made, there are useful data in both of these studies and we need to share that information with prescribers and consumers, and keep Wendy's point in mind, that the bottom line is what is best for the person with arthritis.

DR. HARRIS: In my particular case, I certainly feel that there should be further studies. I have to think that as a rheumatologist, as any physician really, since one isn't sure -- and I can't say hearing anything today makes me absolutely sure whether or not we are seeing a protective effect from naproxen or whether or not there is some sort of excess cardiovascular mortality here -- what does one do if you are confronted with a patient with rheumatoid arthritis, which is a population at increased risk, or with some other cardiovascular one, two, three events and you are being asked to prescribe this drug? What is your comfort level doing this? Do we need to add low dose aspirin? Then, if we do add low dose aspirin, will we cancel the effects of the COX-2 on the GI tract?

I would say that there are enough queries raised with some of the data that we have seen today, enough unanswered questions with respect to cardiovascular events here, that I really do think that some form of further studies should be done.

DR. WILLIAMS: I have to agree with Dr. Wofsy, there is always a need for more studies but this question has specifically to do with cardiovascular events and I would think that there were two particularly interesting things that I think need further investigation. I have never considered the non-steroidal anti-inflammatory drugs as cardioprotective, and we heard data that suggested that at least one of them may be cardioprotective and we have only got any data at all on three of them, and there are 18 or 20 that are out there. So, I do think we need to know what level of cardioprotection is available from the various NSAIDs.

The other one is whether or not there is an effect of the COX-2 inhibitors that promotes thrombosis. While there has been a suggestion, I don't think we have the answer to that yet at all either. So, I think that is another area where further studies are necessary.

DR. SAMPSON: In terms of new studies, I would concur that further studies are needed. I would concur with Dr. Nissen that there should be placebo controls in those. Low dose aspirin should be a factor in the studies. There should be well chosen NSAID comparators that are meaningful in a broad way. The populations -- I would imagine you would want more than an RA population; you would want a broader population. And, care and thought should be put into the endpoint that one wants to look at and the study duration.

In addition, I would go back to what Dr. Wofsy said, and that is that there is a lot of information in the CLASS and VIGOR studies and that there is a wealth of opportunity for people that would like to do some sort of meta-analytical work combining those two studies to try to tease out a stronger effect, or to tease a stronger inference. I don't think we should discard the fact that we have a lot of rich data before us that might provide answers -- some answers, partial answers under further analysis.

DR. ELASHOFF: Yes, I do believe there is reason to be concerned about cardiovascular event risks for the COX-2 inhibitors, and I think the one thing I want to add to what has already been said is that further studies need to be done in a timely manner. We don't want to spend a lot of time waiting around until we have a better idea of what is going on here.

DR. HARRELL: I will just echo what the last two statisticians said. I think the FDA could also provide maybe a little more guidance in terms of the number of comparators needed in the study and which comparators, duration of follow-up and when, in the course of drug development, the long-term safety studies are needed to be done.

DR. HARRIS: An equally different question, in my mind, is does this finding warrant consumer/prescriber awareness? Again, it takes time but I would like to sort of seek opinions of each individual here.

DR. WOLFE: This time I want to actually address some of the comments that were made this morning regarding gastrointestinal hemorrhage. This is an impromptu little presentation --

DR. HARRIS: Can we hold that for question two because I presume question one is talking about cardiovascular events?

DR. WOLFE: That is fine.

DR. HARRIS: We are still on question one, the second part of question one is, does this finding warrant consumer/prescriber awareness? This is with respect to cardiovascular events.

DR. WOLFE: Yes, I think at this point, from what we have seen, there is enough information that is available, going just on the merit of the study itself -- we have to see what the study showed. The study showed that there was a potential increased risk in thrombotic events, particularly for those who are predisposed.

But the biggest message I have, and I mentioned this yesterday, is that the consumer must be warned very, very carefully by physicians that these drugs are not replacements for aspirin for cardiac prophylaxis.

DR. PINA: Agreed on both fronts.

DR. NISSEN: I think that the question for me is whether there is any evidence here of an excess event rate over placebo, and it is just not on the table. We just don't have any want to answer that. So, what can we say? What we can say is that in this population getting naproxen was associated with a lower cardiovascular event rate than getting rofecoxib. Therefore, it seems to me that what we probably need to do, since we don't really know, is to make it very clear that there is not a cardioprotective effect for the COX-2 inhibitors, and that the decision on whether or not to co-administer aspirin is a matter of clinical judgment. I don't think that any guidance beyond that is possible based upon the data. We don't have the data we need to actually make a final determination of with what we saw was cardioprotective effect of naproxen or excess risk for rofecoxib, and I just think we can't go beyond what the data actually tells us.

MS. REEDY: Is that a yes or no?

DR. NISSEN: I do think we should modify the current statement but I would be very cautious about how we modify it so that we do not overstate the issue of risk.

If I could just amplify on that for a moment, we saw a very strong message about some reduced incidence of GI effects and I happen to share Dr. Wolfe's perspective that these are not trivial events. As I said yesterday during the discussion, to a patient it doesn't matter whether you end up in an intensive care unit with a big GI bleed or whether you end up in an intensive care unit with a myocardial infarction. They are both pretty bad things to have happen. So, I don't want to throw the baby out with the bath water here. What I want to do is say what do we know? We know that there is not a cardioprotective effect for COX-2 inhibitors and we should emphasize that in any revisions that are made to labeling, but beyond that I am not willing to make any statements yet.

MS. MCBRAIR: I do think there needs to be some additional information for consumers on the issue of the cardiovascular problems. I would like to see additional studies done. I agree with Janet, and I would very much like that to then help us better guide patients and their doctors.

DR. WOFSY: I have two comments, and I fear they may sound contradictory. I am going to try very hard to make it clear that they are not in my mind.

The first is a direct answer to your question. Yes, I think that the labeling should reflect these concerns. The second, however, is that I think we are making the mistake in the way we are approaching this , that we would be concerned if somebody came forward to us with this question. We are starting out by focusing on a

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question that was not the primary endpoint of the study. It has been picked out among hundreds, maybe thousands of things that might have fallen out unexpectedly from this study. So, we find ourselves going around the table talking about whether the label should talk about the cardioprotective effects of non-steroidal anti-inflammatory drugs, and that was not the goal of any of the studies that we have seen.

So, having already said that I share the view that one of the things that has come out of this study is a reminder that that is probably an important thing to alert people to, I don't think this should be our starting point for discussion. To just follow through with what the statisticians have emphasized in this meeting, from a purely statistical and methodological point of view, this was not the focus of the study and it is hazardous to make it the central focus of the beginning of our discussion. Frankly, I think we need to be starting with what the prespecified primary endpoints were, and then move to what other things have come out of this that have raised questions in our mind that this study was never designed to answer in the first place.

DR. CALLAHAN: I do think the data warrant providing information to consumers and provides. I feel like if the information is out there with all the caveats that it isn't definitive but at least to let people know what is known today.

DR. HARRIS: For myself, I too believe that there should be some things in terms of consumer awareness. I toyed between lack of a cardioprotective effect and actually stating what the results were. But, then we only have that with respect to one of the two COX-2 inhibitors. What does one do about another? So, I would waive with respect to the cardioprotective effect.

But, following Dr. Wofsy's remarks, here is the issue with respect to these safety studies, period, because you apparently start off with -- I think in this case quite justified because GI toxicity is so important with respect to non-steroidals that you could say, yes, let us start off with a safety study with respect to GI toxicity. But the question is to what degree do other organ systems impact these studies, and to what degree should we be monitoring other organ systems? I think this is really muddy waters and I really think maybe at a separate point the FDA really does need to think through some of these issues with respect to safety trials in the future.

DR. WILLIAMS: Interestingly, I agree with everyone but I consider myself a "no." I agree, I don't think we have enough data to make any awareness to anyone yet, other than to say they are not cardioprotective which has never been proposed, at least in my mind, until I got this information. So, I do not think there is anything that we can say yet to consumers or prescribers that has any foundation.

DR. SAMPSON: I guess I would stay with Dr. Nissen's point of view, as I heard it, in that there would be a statement about the lack of cardioprotectiveness of COX-2's, plural. Did you use the word "unknown effects" or aspirin, or left it to the physician's judgment?

DR. NISSEN: Yes, something to that effect. I mean, I think the word crafting obviously is a subject to a lot of discussion.

DR. SAMPSON: But the notion that even aspirin is questionable to counter the lack of cardioprotectiveness.

DR. NISSEN: Right, we don't know what the risk or benefit of adding aspirin is.

DR. ELASHOFF: I think I would feel that something stronger than just saying there is a lack of cardioprotective events is warranted, although it is true that there are many other possible safety things that could have been looked at, and there is no p value protection, the p value was not just sort of 0.047; it is quite marked. There is consistency across several different similar diagnoses within this study. There is consistency with some of the Phase III data. There is consistency with yesterday's data. So, I think while one doesn't want to claim that something has been proven at this point, there is more than just one piece of evidence and they all kind of tie together.

DR. HARRELL: I agree strongly with what Dr. Elashoff just said, and I think that the price of having only one comparator in the study is that we only have the good safety data against that comparator but there needs to be very specific and strong safety warning in the labeling with regard to cardiovascular risk against naproxen. I would go a step further to say that the FDA should consider a labeling restriction with regard to cardiovascular risk factors. Until the other study is done, if it is ever done, the best data that we have now is that patients that have cardiovascular risk factors, of which age is a strong one, may be at risk, extra risk. And, I think there needs to be an assessment somehow according to age and number of risk factors beyond which the patient is an unsuitable candidate for the drug.

DR. CRYER: Dr. Harris, if I might chime in on this at this point --

DR. HARRIS: Go ahead.

DR. CRYER: Thank you. I have sat and kind of listened to the discussion that has gone around and even though I am not a cardiologist, from a consumer and prescriber perspective, all I have heard is that really there seems to be most definitively not a cardioprotective effect that is provided by the COX's and that the strongest recommendation that I think one can make on the basis of the data, at least that I have seen, is that in people who required cardiovascular protection with low doses of aspirin should be given low doses of aspirin.

I heard placed out for discussion that maybe it should be stated what the results actually were with respect to cardiovascular issues, and at least the concern that I have with respect to that is that we, as a group of experts or you as a group of experts with respect to this issue, haven't been able to decide what the data say. So, that would make it even more confusing for a prescribing physician or even more so for a consumer to actually reach a conclusion with respect to the data if you were actually going to include it.

Finally, from a gastroenterologic safety perspective, again I want to just ditto the comments of Dr. Wofsy in that the whole emphasis for the development of these compounds was really because we had a safety need with respect to gastrointestinal events with traditional NSAIDs, and with regard to cardiovascular potential warnings I don't want us or the prescribing physician to potentially lose sight with respect to the data that we have seen today what, in my opinion, is a clear gastrointestinal benefit.

DR. HARRIS: Actually, this question has a third part but my sense -- and I am going to turn to the FDA -- is that we have gotten consensus and enough information that would guide the format. Unless there are any burning views otherwise, I want to go to number two.

I am going to proceed to question number two. Given the potential effects of concomitant aspirin use on GI and cardiovascular outcomes and the large population of patients for whom both anti-platelet and analgesic; anti-inflammatory agents are indicated, what guidance should be given at this time regarding the concomitant use of aspirin and Vioxx? There is a second part, are additional studies warranted? I guess, Dr. Wolfe, maybe we could start with you.

DR. WOLFE: Thank you.

[Slide]

As I said to the group, many of us here in gastroenterology feel like Rodney Dangerfield in that enough emphasis is not being placed on upper GI hemorrhage. I actually agree. I think that we should have started with the primary objective of the study, but the prerogative of the chair was to start with the other topic first.

But, again, this is not a trivial issue. If you look at mortality for upper GI hemorrhage, it is 8-10 percent and it is unchanged since early 1930's. Now, that implies that we are not doing any better with all the fancy equipment we have. I should also stress that we have some real experts here on GI hemorrhage who have done many studies and are true experts in this area so I will be quoting some of the work that they have done.

But one of the reasons that it hasn't changed is that we are seeing sicker people survive longer, and also we are seeing people just live longer and mortality and age are related logarithmically.

[Slide]

I just concocted this real quickly, just using a 10-year old with a bleed which is a little young, but actually I have seen 20-year old NSAID bleeds. If you look, you start with 1X. You go quickly to 2, to 4, obviously to 8. You really increased quite significantly and we are seeing people who are much older have these problems.

[Slide]

The other thing, after talking to some of the cardiologists here, is that mortality from GI hemorrhage is similar to those patients who are actually hospitalized with acute myocardial infarction. Now, MI is a very sexy disease where, you know, GI bleeding is dirty.

[Laughter]

But I tell you it is very, very serious.

Additionally, and I mentioned this yesterday, 13 percent of upper GI bleeds are associated with MI. Steve mentioned before that a patient is hospitalized either with a GI bleed or MI but they could be with both. Believe me, we all see it all the time. This is not trivial. Some people who die at home with an MI or CVA maybe had a GI bleed precipitating the problem in the first place.

Risk factors for mortality include age and concomitant serious illness, as I mentioned, similar to the proportion of the population of patients receiving NSAIDs.

[Slide]

These are the risk factors, but what always comes out are previous ulcers and age.

[Slide]

This is one of many, many studies showing this and it is logarithmic. We start seeing increase in mortality by age from the late 20's and it reaches statistical significance in the early 50's. But, you can see in this group between 70 and 80 the relative risk is 5.6. That is the population with a lot of NSAID use.

[Slide]

I am almost done. Most common GI emergency by far is upper GI hemorrhage. At least 50 percent of GI bleeds are due to ulcers, and we see the vast majority of ulcer bleeds associated with NSAID use, in this 80 percent range.

Thus, just three reasons explain excess mortality due to NSAID-induced hemorrhage. First of all, the elderly use NSAIDs more commonly. Age is a risk factor for NSAID-related ulcer bleed. Mortality due to hemorrhage increases with age. So, it is a significant problem which is the reason the study was done in the first place. We can't lose sight of that. Thank you.

DR. HARRIS: Thank you so very much, Dr. Wolfe. I am going to ask you the question again --

[Laughter]

-- what guidance should be given at this time regarding the concomitant use of aspirin and Vioxx?

DR. WOLFE: I looked at this question very carefully and that is one reason I gave this. There are no data in the study to look at this. So, everything is conjecture; it is hypothesis. That is one of the reasons I think the second part of this question, are additional studies warranted -- absolutely. We have to see what happens. Do we lose the protective effect to the GI tract by adding aspirin? Actually, my last slide was, indeed, showing that aspirin at low doses, as we mentioned yesterday, carries a risk of 2.3. There is no reason to suspect that using a drug which potentially could increase thrombogenic effects would counteract this. The effect will be on the platelet itself to decrease thromboxane and the bleed will then probably occur. So, this is all conjecture, all hypothesis. I don't think we can say anything about the concomitant use but I would like to see that study done.

DR. HARRIS: Dr. Cryer?

DR. CRYER: I agree with Dr. Wolfe's comments, but with respect to your specific question about additional guidance, I just reviewed the current label with respect to the current guidance that has been given and what you say under aspirin is concomitant administration of low dose aspirin st Vioxx may result in an increased rate of TI ulceration or other complications. Based upon the data that exist, I think that is all we can currently say, and I think it has already been sufficiently said.

DR. HARRIS: Thank you very much, Dr. Cryer. I am going to go around the room and ask for brief comments with respect to concomitant use of aspirin and Vioxx with respect to guidance.

DR. PINA: I think that clinical judgment is going to have to be the rule for the individual clinician with an individual patient. Putting in a sort of balance the risk of bleeding, the need for concomitant aspirin, how salient are the cardiovascular risk factors, and how bad the need for the discomfort and the pain associated with the arthritic process, this study talked about rheumatoid arthritis. The drug has not been approved for rheumatoid arthritis. I think it is being used primarily for osteoarthritis even though I am sure there are patients out there with rheumatoid arthritis that are using the drug, and maybe the postmarketing people can tell us that. But, I think in the context of what we are seeing it is going to have to be the individual judgment of the clinician, weighing the benefits of relieving the pain and the discomfort to the patient versus the risk of cardiovascular events.

DR. NISSEN: Very briefly, just a quick correction to Dr. Wolfe's comments, it is really not that myocardial infarction is a sexier disease than upper GI hemorrhage, it is really that cardiologists are sexier than gastroenterologists --

[Laughter]

-- so just to be clear about that. If there is one thing that we can say for sure, is that aspirin is good. You know, studies like the PPP trial, which was very recent, show once again in a group of people with not very many risk factors -- just had that one risk factor including age, there was a striking reduction in cardiovascular morbidity and mortality when you give aspirin. So, you know, probably a lot more people ought to be on aspirin than are on aspirin and I think that is a general public awareness issue.

I don't think we can give guidance here because we just don't know. So, the best we can hope for is the statement that says something like what Dr. Pina said, which is that clinicians must weigh the cardioprotective advantages of aspirin with the potential concomitant risk of increasing GI hemorrhage when these agents are combined because we don't have hard data to say anything beyond that. We just don't know. But let's not forget that aspirin is a good thing for people. I think, unfortunately, it is good for the heart and not so good for the stomach, and that is a really big problem.

MS. MCBRAIR: I do feel that there aren't studies warranting any great change in what we say, other than that it is the clinician's decision as to how best to proceed. I do think we need additional studies.

DR. WOFSY: A couple of quick points, first and maybe foremost, I have been aware for years that cardiologists and gastroenterologists were richer than rheumatologists but I am disturbed to find out that they are also sexier.

[Laughter]

Just a couple of quick points. I agree that the labeling already says what is accurate about aspirin and doesn't need to be changed. In a few moments, I am sure we will discuss the sponsor's claim that they have shown a benefit with respect to GI complications with their drug in people who are not on aspirin. And, if we concur with that conclusion, then absolutely the next question with regard to the GI tract is, is that benefit undermined by concurrent use of aspirin in people where it is indicated? So, that is going to be an important question to answer, assuming we accept the claim that has been put before us.

DR. CALLAHAN: In answering this specific question, I agree with what Dr. Cryer said, that we don't have any more information to warrant changing what is already in the label.

DR. HARRIS: I am persuaded by what Dr. Cryer said. I mean, there is something already in the warning label. I think the worry I have is again the issue that a number of patients who could be potentially on this drug are probably going to be the sorts of patients one wants to put on aspirin, and the question is what does one do with that, given that we have no data with respect to the combination of Vioxx and low dose aspirin that we can rely on. I actually leave to the FDA to decide exactly how they will deal with wording that.

DR. WILLIAMS: My bias prior to coming to this meeting was that if you added aspirin to a specific COX-2 inhibitor you eliminated the unique benefits of the specific COX-2 inhibitor. I have heard nothing in the last two days that would change that bias. So, if they wish to change that bias they need to do additional studies.

DR. SAMPSON: Obviously there is nothing in the data in VIGOR that allows us to make a conclusion about aspirin and Vioxx. Further studies warranted? Clearly, yes. I just want to throw in a reminder. Yesterday, when we looked at the CLASS study and we added aspirin to ibuprofen we got this paradoxical result and maybe a data anomaly, but there was something that people should be aware of.

DR. ELASHOFF: Clearly, to address this question we need additional data.

DR. HARRELL: Just on one comment you made, Allan, I think we have to remember that aspirin in the study yesterday means cardiovascular risk factors as much as it means taking aspirin. But I would suggest we need additional studies and I would just remind everybody, as though you didn't already know, that a single 2 X 2 factorial study is worth more than two two-arm studies.

DR. PINA: I would like to add one caveat to the clinician that we are trying to give some advice to, to remind them that these effects may be incremental the longer the patient is on the drug, even though we are certain, and that the doses used in the VIGOR study were higher than the doses that would be ordinarily used in practice and that, in fact, have been approved for osteoarthritis. So, we are dealing with higher doses and perhaps longer duration of drug administration than may be used in practice.

DR. HARRIS: I am not going around the table with respect to are additional studies warranted, but yesterday we did see the combination to some degree, of Celebrex and low dose aspirin, the question is when one asks are additional studies warranted specifically with respect to rofecoxib, whether or not there is a sense that additional studies or what is there already is sufficient. So, I will ask for a show of hands this time with respect to the question I raised, which is are additional studies required with respect to rofecoxib and low dose aspirin as stated here? I am going to ask whether or not we could have a show of hands, yes or no.

DR. WILLIAMS: The problem is that there are always new studies warranted, and that is the comment that Dr. Wofsy made earlier and I think we can always say that. I think that we have data now. Unless they want to change the fact that aspirin eliminates the benefit, I don't think there are additional studies needed. If they wish to show that they are beneficial in the face of aspirin, they would need to do additional studies.

DR. HARRIS: That is a no. Are there any yes's?

[Show of hands]

MS REEDY: Seven.

DR. HARRIS: Are there no's?

DR. WOFSY: If you are defining Dr. Williams' comment as consistent with a no, I am a no. If you are asking would I like that information, I am a yes.

DR. HARRIS: Remember, all we are doing is providing guidance so we take it in that spirit.

I want to go to the third question, considering the results of the VIGOR trial, do the current NSAID-related target organs for toxicity in the current NSAID template remain applicable? In parentheses there is GI, renal/fluid retention, hepatic and skin. Please discuss. I will open for discussion.

DR. WOLFE: I am comment only on the GI because that is what I am here for. I am a firm believer in setting forth the hypothesis, designing a study appropriately, checking the results, and if the results match your hypothesis your primary goal has been achieved. I think the data both presented by Merck and by the FDA show that there is, indeed, a decreased risk of GI toxicity associated with the use of this drug. No matter what arguments can be made about, well, was it because of naproxen being the comparator -- I don't know. The study was designed. It was approved by the FDA. I think we have to go with what the results showed. I think in that regard I have to say that there is decreased risk of GI events. Endoscopically as well as outcomes show a parallel decrease in the rate of GI complications.

DR. HARRIS: Could I take it that by saying so you are saying the results, with respect to naproxen, are generalizable to other non-steroidals?

DR. WOLFE: No, you can't say that but, on the other hand, this is one of the difficulties of yesterday. Until the FDA establishes recommendations or guidelines for these studies we have no choice because otherwise you can come and say, well, that one didn't show it so you can change the label because it could be that they are safe for other drugs. The burden of proof has been achieved as far as I am concerned. There was a study which was designed; the hypothesis was tested; the results actually warrant a change, I think, in the label saying that the studies done to date show a decreased risk of upper gastrointestinal hemorrhage and ulceration.

DR. WILLIAMS: I agree with Dr. Wolfe that I think they have met the burden of proof. Now, I don't think a single comparison is generalizable to all NSAIDs but I think they do have to change the label to say that in the one study that was done it was shown to make a difference. As opposed to the other three systems that were mentioned here, I don't think there is anything to suggest that anything needs to be changed in that part of the label.

DR. HARRIS: Can I make a comment before you do, Dr. Elashoff? Could we then say that we could make a similar remark with respect to Celebrex versus ibuprofen because, of course, there was an advantage there?

DR. WOLFE: I will respond to that. Again, you have a primary goal. You have a hypothesis. You have an objective. If you meet the objective statistically -- you have ground rules. FDA has ground rules. Don't you have ground rules? And, if the ground rules show -- studies are not designed in a vacuum. They are designed with your input. If the goal is achieved, then you can say what the goal was and what it showed. If you don't show it, you can't say it.

DR. ELASHOFF: I don't see any reason to change what is said with respect to the GI. This was only one NSAID. The rate was about 2 percent, and what is stated on the template is a rate of 2-4 percent. So, that is consistent with that rate. As I said yesterday, there is no evidence that some purported advantage to this shows up as an overall advantage to the patient because, in fact, there is a significantly higher overall adverse event rate for this drug. So, I don't see any reason for changing the GI template.

DR. WILLIAMS: In response to your previous question to Dr. Wolfe and me, I would agree that with

Celebrex you could report that it also showed a benefit opposed to ibuprofen. You could also say that there was no benefit when compared to diclofenac because you have data on both drugs.

DR. NISSEN: Well, I am just a poor cardiologist so I don't have a lot of sophistication about the GI tract, but it seems to me that we can't make this like it is in the Olympics. When you pole vault, you know, you go over a height and then somebody comes around and says, "well, okay, you made that height; we're going to put another bar up for you to go over." I mean, it seems to me the sponsor here did a very large, probably pretty expensive study, with the advice and consent of the FDA. They created this template of goals. They made those goals very clear from the very beginning. They achieved not a marginal amount of statistical significance on the GI side but an unequivocal statistical significance. So, the statement that rofecoxib is safer, from the gastrointestinal point of view, with respect to the endpoints that were used over naproxen is a fact, in my view, and not a marginal one, and I think that should be reflected in the product literature.

So, just as I think there is uncertainty on the cardiovascular side, I think you can't keep raising the bar here forever. I think at some point you have to say this is proven, and I was convinced by the data. We can't say anything about other comparators, nor should we, but I think we can state as a fact, or it can be stated in the product literature that in a large comparative trial, compared to naproxen, there was enhanced GI safety.

DR. WOFSY: I don't think the public is well served if we approach this discussion on what I view, to some extent, as technicalities even though they come close to my heart because they are technicalities that rest on the scientific method and statistical significance.

Let me explain what I mean by that. Yesterday we saw a study that didn't risk to statistical significance with respect to the primary endpoint, and today we saw one that did, and my view is that to distinguish between them, frankly, would be a technicality and would not be a service to the public.

Let me explain, therefore, what I think we have learned in part from the last two days and in part from before the last two days. I made some notes this morning and I think they run through all the comments that have been made. All NSAIDs are not created equal. They exist on a continuum where benefits in one area may come at the cost of complications in another area. And, the results of studies as a result may well depend on which one you choose to compare to, where it is on that continuum. Just to use two medications that aren't before us, for example, diclofenac may have less GI adverse effects than some and be less cardioprotective, and ibuprofen or Naprosyn may have more GI side effects than some and be more cardioprotective.

I think that is the message that is emerging. I think the other part of the message that is emerging is that the COX-2 inhibitors exist on that continuum. They exist at one extreme of that continuum but they exist on that continuum. And, I have been convinced by this morning's data that, at least with respect to some of the other non-steroidals on that continuum, they have less GI toxicity. I also have been concerned that that reduction in GI toxicity may come at a high cost in terms of complications elsewhere.

From a labeling point of view, it seems to me it would be indefensible not to share that information with the public, both pieces of that information. I haven't seen a single thing in the two days from one of these drugs that would contradict things that have been presented in the opposite presentation and so I would hesitate to use a technicality to somehow deal with them differently. It just flies in the face of my understanding of the data that has been presented and my understanding of the science that is at the base of the data.

So, from a labeling point of view, I think it is frankly clear what we have learned from these studies. It is important what we have learned from these studies, and it ought to be shared, I think, in the sense that I have tried to describe it.

Just going one step beyond since the comments I have made speak to the value of what has been done, I should also say that what I have just said is from a labeling standpoint. From a patient standpoint, I think there are very serious questions raised about whether patients who take these drugs would be better served by a cardioprotective traditional NSAID unless they are at high risk for ulcer disease. I am not suggesting that going into the label but I am just pointing out that depending on exactly what you are thinking here and where you are going, you could frame this in different ways. But from a labeling point of view, we have learned some things and they should be shared.

DR. SAMPSON: I agree with you. There is apparent large variation in the NSAIDs. I don't know how that is going to be played out in terms of the labeling by the Food and Drug Administration, but in terms of Dr. Nissen's comment, if we do stick to the technical labeling it would seem to me, as part of that statement about the beneficial effects, you would want to put in something that it was shown only in an RA population and make that very clear, and also that no aspirin was taken and the benefit is very restricted both in population and in the adjunctive use of aspirin.

DR. PINA: I have been going through the labeling template that we have in front of us, and under warnings there is this whole list of gastrointestinal warnings. There is a list about anaphylactoid pregnancy, hepatic, renal, hematologic, asthma, fluid retention, edema and there is no cardiac. The cardiac is tucked back here where additional adverse experiences have been reported. So, I think this warrants a paragraph up here, sooner rather than at the bottom, about the observations made in this trial about the risk of thrombotic events.

Now, having said that, I agree that the sponsor has proven what they meant to prove in a restricted population of rheumatoid arthritis patients who had no aspirin. And, I think any way you turn around that data versus naproxen, it is very restrictive. I agree with what Allan said. What they set out to prove in a very restricted population is true and I think the public needs to know that. At the same time, I want to see the paragraph about the cardiac events. Then the rest, as we normally do, we have to leave to the clinician to make the decision.

DR. HARRIS: Let me interpose at this point that, in fact, the issue of the cardiac events and whether or not that should be included is something that I think is worth a word or two. But I really would like to settle the GI events. In other words, the question is should there be a change to the template.

I wonder if I might get a chance to make a comment and then we can keep going, for what it is worth. But, you know, I must say that there are, from my perspective, non-steroidals and non-steroidals, and there is clearly a spectrum of GI toxicities. Had yesterday, and I hate saying so, the choice been ibuprofen and naproxen instead of ibuprofen and diclofenac, I guess the sense would have been something very different. And, today, had it been that the sponsors decided to choose naproxen and diclofenac then, because we saw a meta-analysis, by the way, where diclofenac looked like it came in at about the same level as rofecoxib -- and I think there is, indeed, a general question that Dr. Wolfe raised today and it has been bothering me because on the warning label you are really making a statement in comparison to all non-steroidals, and that makes the assumption, with respect to GI toxicity, that they are alike and perhaps they are not.

So, really we can't go back and redo these studies today but the issue is in the future when one is designing studies like this what advice should be given in terms of comparator drugs because, again, we are struggling with the issue and we will continue to struggle with the issue. You know, which drug is best representative of the non-steroidals? Is it one? Is it two? Is it three? It goes on and on, and I think it is very bothersome and very different for us to make a decision here.

DR. DELAP: I think my immediate reaction to the last thing you were saying as to choosing which drug to compare to, and that has been a theme of some of the comments, I kind of hate to say it but the reality is we would probably come back to you and ask you what you think is the drug that we should be comparing to so that we can tell our sponsors and have some public discussion of that.

DR. HARRIS: I will agree with that.

DR. NISSEN: Nigel, I hear what you are saying -- what would have happened; what could have happened had the CLASS study used a different comparator, but we don't have that. We have what we have, and the comparators that were chosen are the ones that were chosen for whatever reasons they were chosen.

Let me ask a rhetorical question. Are we going to ask the sponsors of these drugs to go do 8000-patient studies for each of the dozen or so potential comparators before we agree that there is some benefit? It is not going to happen. It is not reasonable to make it happen and, therefore, we have to tell people what we know.

Let me tell you that I learned a lot today as a cardiologist, a lot about the GI tract that I didn't know before, and what, of course, is going on here is what Dr. Wofsy refers to as clinical judgment. You know, I actually prescribe these agents to cardiovascular patients so now what I am likely to do, and what I would like to share with our community is a knowledge base that says that if you have a patient that is at low risk for cardiovascular events, a younger person perhaps without co-morbidities, they may be better served by an agent that has better GI protective effects, that is, is less likely to result in GI morbidity. If I have a patient who has had four prior myocardial infarctions and a couple of episodes of unstable angina, I am going to think twice about giving them a COX-2 inhibitor certainly without aspirin.

So, the real question for us is how do we communicate the message from the trials that we have heard in a fair, balanced way that allows a clinician to weigh the risks and benefits of the classes of drugs available to them and choose a drug that, in their hears and their conscience, is the best drug for that individual patient? So, I favor statements of facts in the labeling as we know them. I like the way you, Allan, revised my comments about what do we know. We know that for this population the naproxen event rates in the GI tract were higher than they were for rofecoxib, and we know that cardiovascular event rates were higher for rofecoxib than they were for the comparator.

So, I think that what we really need to do is to provide some kind of a balanced view of what the studies showed and then let the physicians use their clinical judgment to pick the agents that they think make the most sense for their individual patients. Beyond that we can't guess at what another comparator would have shown because we don't have that data and we are not likely to have it in the near future or even at any time in the future.

DR. ZEGER: I agree with your point that what we really have to do is think about what evidence is available. What I don't hear being talked about at all is the evidence that came from careful analysis of the OA population and to compare it to what we have learned in the RA population in this trial and if I could just very quickly for the committee --

DR. HARRIS: I am going to have to say no. I am sorry but I am going to have to say no.

DR. ZEGER: Let me just conclude that what I see there is a relative risk with a diverse set of comparators of 0.54 or 0.45 in the OA population and a relative risk of 0.46 in the RA population for a different comparator. So, I think when you think about what is the presentation of evidence, it is important to think about all the studies that have been done and not to dismiss some because they were done through a series of trials rather than just one trial.

DR. HARRIS: What I am going to ask now is whether or not, in your opinion as I am going around the room, you believe the warning label should be changed with respect to GI toxicity. Keep your remarks brief, please, because I think most of you have had an opportunity to make a statement. It really is mostly yes or no in a quick way. Dr. Cryer, though you are not a voting member, let the record show that I am going to start with you.

DR. CRYER: Thank you, Dr. Harris. One of the things that I have actually learned from this body of literature and this process, and I think one of the things I actually feel strongly about with respect to informing the consumer is that there is a continuum with regard to NSAID toxicity. I think if you are going to make labeling changes that needs to be a very clear message that gets relayed to prescribers and to consumers because I absolutely agree with you, it is not just NSAIDs as a group. All NSAIDs aren't the same. So, the continuum message clearly needs to be in there.

But I actually also fall in agreement with my colleague here, Dr. Wolfe, and that is that with respect to these labeling considerations what drives the label is a process, a process that you define ahead of time, and there are rules that are inherent in that process that drives the label. So, I personally don't really see these issues as technicalities because you have to have a process and rules that actually drive what ultimately goes into a label. So, the two points in terms of how I see it are that there is a continuum issue and I think you are obligated to put in the label the results you have with respect to the studies that you have designed based upon prespecified rules.

DR. WOLFE: I don't want to be repetitive but I am a little disturbed. Again, there are rules and the rules are established and if you play by the rules, then you are rewarded if you are able to meet your primary objective. I feel very strongly about this, if you are going to mention the cardiovascular warnings in there because you found some potential cardiovascular effects and you don't mention the fact that there was a protective effect on the GI tract, I think you are being remiss because you are misguiding people to say there may be a drug out there that doesn't cause ulcerations much. So, I really think if you are going to do one you have to do the other. If you are not going to do one, then don't do the other.

DR. PINA: We are addressing right now the GI effects.

DR. HARRIS: Absolutely.

DR. PINA: I have read the section on the warnings. The section on the warnings looked pretty narrow to me and I don't think there isn't anything here that isn't a fact, including that patients who have a prior history of ulcer disease are more prone to have spontaneous bleeding with these drugs. I don't think there is anything in here that is any different since it is generic for NSAIDs.

I would add, however, a statement such as in so many patients with rheumatoid arthritis Vioxx has shown such-and-such a reduction in GI events without concomitant use of aspirin at doses of such-and-such -- just a statement stating exactly what was proven here. The rest is very generic and is valuable information that I think clinicians should read because that applies to non-steroidals, period.

DR. NISSEN: I would change the label. Again, the term that has been used about the study is that there is a technicality involved. To me, a properly designed, prospective, blinded, randomized study with a strong p value can't be viewed as a technicality. So, for that comparator in that population there is very strong evidence and, therefore, the labeling should reflect the strong evidence that is available. Beyond that, I can't say anything else.

MS. MCBRAIR: I think the label should reflect exactly what we know and what we learned from the study that was done.

DR. WOFSY: I had hoped to just say yes but I also have to sort of regret my own choice of the word technicality, which has deflected some of this discussion because I don't believe I meant technicality in the sense that it has been interpreted.

I just think the following, yes, I think the label should be changed to reflect -- and I am not sure or where, to reflect the proven advantage demonstrated with respect to GI toxicity in this study and to reflect the concerns that have been raised about what price may be paid for that advantage.

What I meant to imply by technicality, and I will just comment on it now but that will obviously be the FDA's decision, I wouldn't know how to implement this myself, is that I would think it would be a disservice if what came out of the discussion for the last two days was somehow to imply to the community that there is a difference between the agents we have talked about. There is a difference in what has been proven in some statistical sense, but I have not heard a single thing that would lead me to believe, as a clinician, that I have strong evidence that there is a fundamental difference either in efficacy or toxicity. How that is reflected when you go to write it, that is your problem and not mine. And, that is really all I meant by technicality.

DR. CALLAHAN: I agree with what Dr. Cryer said about the continuum. I do think that is an important issue to be reflected. I said earlier in the day to Dr. Wofsy that the main message to me is that all NSAIDs are not equal and there definitely is a continuum. I did like the way Dr. Sampson revised what Dr. Nissen had said about reporting of what was actually found in the study and having the label reflect the evidence that we do have out of this study.

DR. HARRIS: I am going to give a reserved no, I don't think it should be changed. I think that as a treating physician, if the label were just generally changed like that, the sense that I would have is that this agent is better than the non-steroidals, and I don't think that is what has been proven.

Given the labels, such as they are with respect to these agents, I, therefore, don't feel that there should be a change. At the same time, I do think that this data, with respect to naproxen in this particular group of patients with this particular agent, is worth communicating in some way within the label. But, I want to add one other thing. I think too if I feel this way I would have wanted, actually, the same thing to be done for celecoxib because, again, these are two massive studies, the CLASS and the VIGOR today and it just happened to be a choice of agents, and so on, and I think if we are going to report, then let us report the results such as they are.

The third point I am going to make is this we respect to labeling, I really do think that the time has now come for the FDA to look at this issue with respect to comparator and non-steroidal agents because we are taking one or two agents and generalizing, and there are obviously issues with respect to that. I don't know if it is ever going to be answerable but, nevertheless, I think it is worth a discussion.

DR. WILLIAMS: I will give Dr. Wofsy's yes.

DR. SAMPSON: A cautious change is probably in order. I think the continuum message has to be delivered. I think the wording has to be done in such a way as to not imply that this applies to all NSAIDs. Then, I made a little note to myself, as Dr. Harris was speaking, about the issue of celecoxib and whether there is some way of working out in all of this class labeling for COX-2's that would be equally applicable, and somehow summarize the information gleaned from both very large studies.

DR. ELASHOFF: I agree with Dr. Pina that I don't see any reason to delete anything that is already there. I guess in view of that, I probably would feel that people could learn about the results of this study in some other way than the label but if it is strongly felt that the label should include some very cautiously worded sentence about the results of this trial, I wouldn't strongly object to that.

DR. HARRELL: I would change it. I would be narrow, be specific, report the good with the bad. I do have to add though a p value is a technicality. It is a mathematical convenience and allows you not to think. One statistician, Herman Rubin, called the p value, next to the atomic bomb, the worst invention of the 20th century.

[Laughter]

DR. HARRIS: Yes?

DR. DELAP: I think we spend a large amount of time with sponsors on labeling, and it is a very important mechanism for us to communicate with patients and prescribes. It doesn't always communicate as well as we would like but we do the best we can.

I think what drives us a lot in the labeling negotiations is to try and serve the physicians and the patients by giving them the information they need to choose among products. So, if there is a distinction to be made or that we think is pretty likely to be an important factor in a decision of a physician and patient to use this drug versus that drug, then we think it belongs there. If there is terminology that could be misleading in terms of appearing to indicate a distinction, we try to stay away from things that appear to create distinctions or we are not confident might actually exist.

It is coming up here because we had kind of a generic way of labeling NSAID toxicities, and we recognize increasingly as we get more data that there are distinctions to be made. The struggle is to really accurately convey that information, I think, for patients and physicians.

I think, again, the last thing I will say is that we aren't captive, I think, to p values, to follow up on the last speaker's comment. Although p values are a good way of making decisions about data, they are not the only way. Again, I think if we feel that there is information that is relevant and important information we try and include that.

The very last thing I will say is that we struggle with things like making comparisons against groups of drugs where we haven't really studied all the members of the group, and that has been a good part of the discussion here. Again, it would not be fair to paint all of the other NSAID products that are out there in the market that antedate celecoxib -- we can't paint them all with the same brush. In that sense, I am not satisfied that we can really say that we know what we need to know, and just say all of those are there and these two drugs are here.

DR. HARRIS: Thank you. Now I am going to raise the cardiovascular question. What I am going to do this time around, Dr. Pina, if you could give your opinion and then maybe I will ask for one or two other comments and then we could probably, if necessary, have a show of hands as to whether or not they accept some of what you say.

DR. PINA: As far as the cardiovascular events, I do think that we have seen some effects of naproxen on platelet inhibition. I can't say that is not there. But not withstanding that, it still leaves me the concern of a greater rate of thrombotic events than I would have expected in this population, and I value my rheumatology colleagues' comments about the higher incidence of cardiac events in this population but I am still not convinced that we know that percentage well enough to tell me that this population is at a rate that they should be for the amount of rheumatoid arthritis. As I understand the disease, it is also based on the duration of the disease and the severity of the disease, both of which we are not certain about in this trial.

I am also uncomfortable with the doses that are higher. I don't know what the thrombotic events would be in this population if the doses were lower. So, it still leaves me with a fair amount of discomfort even though I do think that some of the differences are due to naproxen. I would put it in the label exactly as that, that the risk has to be noted, that it may be there even in the patients that you would not use aspirin for. That is why I was asking Dr. Villalba about that table that she showed in patients who would not have received aspirin otherwise, and that trend is still there. Again, it may be rheumatoid arthritis. It may be the disease that we are looking at but I can't say for sure. I just don't have that data.

DR. HARRIS: Yes, Dr. Nissen?

DR. NISSEN: Briefly, I think what I would say in the label is that there was an excess of cardiovascular events in comparison to naproxen, that it remains uncertain whether this was due to beneficial cardioprotective effects of naproxen or prothrombotic effects of the agent, and leave it at that, that basically we don't know the reason. We do know there was a difference. That awareness should be made available to the prescriber and to the consumer, but without necessarily a final judgment as to the reasons for that difference.

DR. WILLIAMS: I thought we addressed this in question one, and I still don't think we have enough data to make a statement. If we were going to make a statement, I would favor the one done by Dr. Nissen but I still don't think we have enough data to make a statement.

DR. HARRIS: Let me see if I can comment here, you know, we have the label such as it is. The actual crafting of the language -- it sounds very crafty, in fact, Dr. Nissen, as to how it might be crafted and it may be crafted the way you say. The question is whether or not there needs to be some additional language, if you will, with respect to that. So, I am going to ask yes or no, whether or not there needs to be additional language, perhaps crafted along the lines that Dr. Nissen suggested, or, no, there doesn't need to be any additional language.

So, let me ask for those feeling yes, that there needs to be something, some additional language perhaps, along the lines of Dr. Nissen in terms of the label. I will ask for a show of hands.

[Show of hands]

Is there anybody against?

[One hand raised]

One against. Any abstentions?

[No show of hands]

Again, let me emphasize this is merely advisory and we are merely giving an opinion here. Thank you.

We are now going to move to question number four. Please comment on the overall safety comparisons between Vioxx and naproxen in the VIGOR study. We sort of commented before, but whether or not --

DR. SAMPSON: There were some other pieces to number three. There is the hepatic and skin.

DR. HARRIS: Thank you so much, Dr. Sampson. I had actually wrongly come to the assumption that perhaps there were no other issues with respect to that but, if there are with respect to hepatic and skin and, in fact, any organ system, is there any additional comment or any change that one might expect?

DR. PINA: Let me make one comment simply because clinically it is what we see and it is what it is. Down in the labeling, where it has "additional adverse experience" there is a mention of congestive heart failure and perhaps there should be a statement about fluid retention in congestive heart failure and about the incidence of congestive heart failure as demonstrated in this trial, rather than just lumping it down here because clinically it is there; clinically we see it.

DR. HARRIS: Can you just quickly read the statement for us?

DR. PINA: I am looking at the template and if you go to page 11, they have additional adverse experiences reported occasionally include congestive heart failure, etc., listed under the cardiovascular system. I think that as potentially this number of patients continues to grow, it is the one cardiovascular disease going up in the country instead of going down and there perhaps should be some statement, and maybe the data from here can be quoted. The sponsor has admitted to fluid retention and edema. I don't it is anything that they haven't. But, I would like to see it singled out somewhere because the sense that these agents are quite safe in patients with volume repletion and volume expansion is not the case.

DR. WOLFE: I have a question. Is that specific for rofecoxib or for NSAIDs in general that we are seeing an increase in congestive heart failure?

DR. PINA: I think it is for NSAIDs in general but there is the common concept out there that these agents may be a bit different in this population, and I think it should be said that they are not different in this population. So, one statement there would be reasonable.

DR. WILLIAMS: What we saw from the data was edema, and that is listed under 1-10 percent and, based on the data we saw today, I am not sure we can make that change and if we did, it should be generic for all NSAIDs.

DR. PINA: But they did have a separate slide for heart failure incidence. That is the one I am talking about.

DR. WILLIAMS: It was not up to that level, or any different than any other NSAID. That is why I say it should be generic if you are going to do anything because, based on the data we saw here, we shouldn't --

DR. PINA: I agree with the fact that it should be generic. I would like to see it in there because it is not a drug without its problems, all of them, in the heart failure population. So, if we do it for one maybe we should do it for all, but I think it should be here separately.

DR. HARRIS: I must say, from my own perspective and I don't want to inference anything, I think this is a general observations for NSAIDs and, I must say, based on the data, it doesn't rise to any greater level than the other NSAIDs requiring a separate statement. So, here is what I am going to say, Dr. Pina, how many people agree with Dr. Pina that with respect to congestive heart failure there should be something additional written in the warning label?

DR. PINA: I agree with Dr. Williams about all NSAIDs, not just this drug, not Celebrex alone. I agree that all of them should have some statement. I am not trying to single this drug out at all.

DR. HARRIS: Do you think it is adequately covered?

DR. DELAP: We are assiduously writing things down here in the discussion and I think we can take that back and think about it. Again, we do try and communicate what we think are the most important points about all these products to physicians and patients, and I think that what we hear from you is that you feel that this may require a little more prominence and we will take that back and look at it.

DR. HARRIS: Thank you. There were other organ systems. Does anybody have any feeling as to whether there should be changes with respect to any of the other organ systems based on anything that we have heard today? I take the shake of heads to mean no, and there doesn't appear to be any yes. So, there seems to be a consensus; no other change. Thank you.

Now, question number four is please comment on the overall safety comparisons between Vioxx and naproxen in the VIGOR study. I must say that this field has been plowed quite extensively already. If there is some statement that you feel might add to what has already been said, then I am going to ask you, in fact, to comment.

DR. WILLIAMS: They actually had a slide that showed serious adverse events and naproxen looked better than rofecoxib in that area.

DR. HARRIS: Given that comment that, in fact, apparently naproxen in overall respect to serious adverse events looked better, is there anything else that one would want to say other than that? Yes?

DR. WOLFE: There is something else I want to bring up that was a little disturbing but, again, I learned something new, that the p value isn't so holy after all.

[Laughter]

If that is the case, then in all fairness to celecoxib, I think if you are going to be so circumspect on the results of the VIGOR trial, saying it was only naproxen that showed a difference, then divide their study up and show the table -- you do it all the time in the PDR -- and show the differences between celecoxib. Again, a lot of us think this is probably a difference in study design that the differences weren't shown in celecoxib. These are clearly two different studies, with very different designs and different results probably because of that -- I am going to stress "probably." We are still not shown why the differences were seen in these two studies.

DR. ELASHOFF: While I think that some mention needs to be made of the overall difference in adverse events, whatever is added for cardiovascular events and whatever is added for GI events, make it clear that there is somewhat compensating size of what is going on there. Then, one wouldn't necessarily need to say anything about total adverse events. But, one certainly wants to avoid a sentence which implies that you get a lot of advantage in GI and only a little extra worry in cardiovascular or something like that, which would hide the overall total rise in adverse events.

DR. HARRIS: Thank you for that remark, Dr. Elashoff. I think it is a very important remark. Can I get another comment or two as to whether or not there may be some value to doing that?

DR. CRYER: This is a concept that actually has been constructive for me over the last couple of days, that while there are, or may be, clear benefits with respect to organ-specific benefits physicians need to keep in mind the overall, global safety. In follow-up to your comment, there may be some reversal of organ-specific benefits when global safety is considered, and I think that is an important message which has been a new perspective for me, in fact, because as a gastroenterologist I have somewhat had tunnel vision with respect to these issues, but I think it is an important message with regard to educating physicians.

DR. WOFSY: I would just concur. Since you are asking for comments, I will bring back three messages to my patients and students. One is that the study confirmed what we thought we knew with respect to the relative benefit of rofecoxib over at least some of the traditional NSAIDs with respect to GI toxicity. I learned that there is reason for concern about thrombotic events and probably the message that you are both emphasizing and that I agree with very much, that, in fact, what came out of that study was that serious adverse events were at least as common, or more common in the rofecoxib group. That is an important part of the message.

DR. HARRIS: What I am going to do is just to carry that message that, in fact, one does have to weigh the benefits of one organ system compared to sort of the overall risk-benefit, whatever. I will actually ask for a vote with respect to whether or not we actually should advise that there might be some way of framing that benefit in one system and the issue of overall benefit. Do I get a sense from the committee that we agree that there should be some mention made of that? Let me have a show of hands, yes or no.

[Show of hands]

Is there any disagreement?

[No show of hands]

Any abstentions?

[No show of hands]

So, that was unanimous.

There are two general questions that have been posed, and I want to read the first of them -- yes, Dr. DeLap?

DR. DELAP: I would just like to say one other thing before you leave the individual drugs. You were talking about the balance as seen in the studies and the last thing I would like to say is that in looking at those, of course, we will be looking also at the fact that both the study today and the study yesterday used kind of high-end doses of the COX-2 drug versus some more standard dose of the comparator drugs. That does weigh in a little bit, although we don't know exactly high, on the exact rates. It is not a direct comparison of the usually prescribed doses.

So, we will have to factor that in as well in looking at those kinds of numbers.

I guess we are moving into the general discussion now which doesn't specifically concern the Merck product but concerns all of the discussions over the last couple of days. I guess we can kind of excuse the Merck folks unless there is some further comment that they would like to make before we move on in our agenda. I mean, you can continue to sit there if you want but you don't have to do anything.

[Laughter]

DR. GOLDMANN: I would just like to thank the advisory committee and members of the FDA for a really stimulating couple of days. Thank you.

DR. HARRIS: I think maybe a ten-minute break would be worthwhile. So, we will reconvene again at 3:25.

[Brief recess]

General Questions

DR. HARRIS: In this portion of the discussion we are dealing with general questions, and I was asked whether or not there might be brief comments invited, as we go along here, from the audience. As long as they are kept very brief and to the point being discussed, I think they certainly would be welcome.

I want to read the first question for the committee. Do these two large outcome trials suggest that,

(a) GI and, (b) overall safety should be addressed similarly with large outcome trials before organ-specific safety comparison and claims can be considered with new agents in the future? That is quite a mouthful.

What I am going to do is invite comment first from members of the committee.

DR. HARRIS: Dr. Harris, just a point of clarification, when we think of new agents here we are thinking of new COX-2? Is that correct?

DR. HARRIS: I am going to ask the FDA. I mean, this was the question posed. I presume it is new COX-2 but let me ask that question. It may be broader than that.

DR. GOLDKIND: I think we could look at it as agents that are proposed to have safety benefits. So, we are not really talking about efficacy; it would be whether a sponsor feels that there is a safety advantage, and how organ specific versus general safety -- how that balances, and how strongly overall safety needs to be examined before specific safety claims since it is not the way we typically see it, typically we are looking for efficacy and then you describe safety in whatever size database you have. The paradigm is a little different here.

DR. SAMPSON: You are not suggesting that we consider this statement for all types of compounds, are you?

DR. DELAP: I was just going to amplify on that

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subject because the NSAIDs is where we have kind of a template class labeling. So, I think the general rules are that if you want to make a claim against some other individual drug, you know, drug A versus drug B, forgetting about the disease and the class of products for the moment, then you have to study drug A against drug B. But, here we are talking about within this NSAID class where we have some kind of standardized labeling information where you might want to make some modifications or comparative claims with regard to that NSAID template kind of information.

DR. WOLFE: You said similarly and I feel very strong some standards should be set. And, as long as I am speaking first, I will tell you what I think the standards should be.

Generally what has been done in the past is to use the comparator which is the drug used most commonly. In this country that is probably ibuprofen and naproxen, those two drugs as the standard comparators in the most commonly used doses. Additionally, in the case of COX-2 inhibitors probably other drugs as well, but I would leave aspirin out of it because, otherwise, you are not going to be able to tease out aspirin very well unless you have very, very large studies, really large studies which then take aspirin into account as a separate group. If you want to look at aspirin, make it a separate study. Otherwise, aspirin is going to confuse your data very, very significantly.

The other point I would make is that having said take aspirin out, in other studies put aspirin in because that is more or a real-world situation but I would have separate studies to assess whether aspirin is a risk factor, and whether it is additive or whether it negates the protective effect any drug might have.

DR. NISSEN: This is really a troublesome question, and I was very persuaded by David Wofsy's comments about the fact that we are talking about a class of drugs that is basically a spectrum, with the COX-2 drugs on one end and maybe naproxen and aspirin and ibuprofen on the other. So, whenever you do a comparison you are picking some point on that continuum between GI, cardiovascular, renal and other effects. So, it becomes extraordinarily difficult to do this.

So, it seems to me that the benchmark probably should be overall safety because when you have competing effects here -- you know, we have said, well, maybe yesterday they used the wrong comparator. Well, you know, the way to assess a drug before you say drug A is safer than drug B, when you know you have that kind of a continuum of benefit and risk is by showing that overall safety -- I can't necessarily define that right now for you but that overall safety is better for one drug than another. What I might do there is classify serious adverse effects and say you have to show that your drug in totality produces less serious effects than another drug before any comparative claim can be made. Otherwise what you do is you pick a drug based upon the endpoint you want. You can pick the right comparator and you can get it to show almost anything you want to show.

DR. WOLFE: So what? Not all the patients are the same. If we have a patient with a previous history of GI bleeding from ulcer disease we want to use a drug that has low ulcerogenic potential. If we have a patient with a previous myocardial infarction, we want a drug that won't cause myocardial infarction. I think the data is as it is. We should know what the toxicity is specifically.

On the first day of pharmacology we learn that every drug has toxicity to it. We have to know what that toxicity is very specifically. I mean, the reason I mentioned specifically naproxen and ibuprofen is because they are the most commonly used NSAIDs right now and they are not at the opposite ends or the spectrum. If you want it for GI bleeding, let's put peroxicam back in there and we will have plenty of really big differences then in almost every drug.

DR. HARRIS: Dr. Wolfe, I am wondering if I could pose a question to you. Suppose that there was some new agent that, in fact, showed in terms of GI toxicity that it was absolutely equivalent to placebo, however, that we found -- and this is an extreme example -- should we ignore the fact that, in fact, it increased renal toxicity to a degree much more than one would expect?

DR. WOLFE: Absolutely now. That is the hole point. There was an NSAID introduced -- I forget which one it was -- that caused hepatotoxicity and the drug was never approved by the FDA because of hepatotoxicity. We need to know what the toxicity is. If it is unacceptable because of other organ systems, then it shouldn't be approved. On the other hand, if we have a drug -- let's pick drug X which has complete cardiovascular sparing effects but has serious gastrotoxicity because of ulcers both to the stomach and the duodenum, that information is important for everybody to know about.

I mean, basically what we are saying is pick your poison. We know the NSAIDs are drugs which have serious toxicity associated with them. We have seen the COX-2 inhibitors and it looks like they may be having a sparing effect on the GI tract in exchange for an effect on the cardiovascular system, thrombogenic events. But, again, every patient is very different.

DR. HARRIS: I am going to invite more comments.

DR. WOFSY:

DR. ELASHOFF: First of all, I would like to say that I agree that the overall safety has to be the bottom line and that I am not sure it makes much sense to talk about it being more safe this way but might be more dangerous in some other way. But, apropos of entering people and now feeling that we could say that since it looked a little safer in GI that our patient who has GI problems would do better on this one versus somebody else doing better on another one, I don't think the data have been analyzed in enough detail, or perhaps even could be analyzed in enough detail to really address the question of whether that kind of assumption is true or not, that you really could differentiate patients and what kind of patients are going to do better on this and another kind of patients are going to do better on that.

DR. SAMPSON: I want to speak just a little speculatively for a minute. I am going to put on my statistician's hat and start to think about models. I am thinking about Dr. Wolfe's comments about a spectrum of NSAIDs, I get the impression that you actually think of things almost linearly laid out, at least not in the kinds of responses they create but that somehow the spectrum is in one dimension. I guess what I am wondering is, and I was asking Dr. Williams about this, could you measure the ratio of COX-1 to COX-2 inhibition fort he different NSAIDs? I gather that is different. Is that correct? Some NSAIDs are much more COX-1 inhibiting and others are much more COX-2. Is that number available for every NSAID now?

DR. WOLFE: There was a paper in Annals of Internal Medicine last January, by Byron's colleagues, Feldman and McMann, which was a meta-analysis looking at about 20 different NSAIDs and looking at the COX-2-COX-1 relationship using in vivo assays. The information is available but I am going to caution you, that doesn't always correlate directly with the toxicity of the drug itself.

The other thing is that you are speaking as a statistician, and the thing is that in so many ways so am I because I am looking at the statistics. We do this every day in medicine. We are looking at the chances of this drug causing a good effect of you being such; the chances of causing toxicity is such. On the other hand, in the individual patient it could be 100 percent effective or 100 percent toxic or zero percent. I am exaggerating, but there is a lot of individual variability. We are looking at a statistic. This is called probability in every single person we take care of that this drug may produce its desired effect or cause a toxic effect.

DR. HARRIS: Yes, Dr. Cryer?

DR. CRYER: I would also like to comment. I think that I would like to steer you away from that concept based on differences in selectivity based upon preclinical data which clearly show that there is a spectrum, probably not linear, with respect to differences in selectivity. But those concepts are flawed in that they are not entirely applicable to clinical outcomes, and that was the entire reason for the development of these outcome trials. We really want to see how the differences fall with respect to outcomes. Unfortunately, we have very few data that actually give us this spectrum information with regard to outcomes.

The other comment that I think is worth emphasizing is that while I think it is important to emphasize that there is a continuum, that concept with respect to NSAIDs, I think there is also a continuum with respect to patients and patients' risk for the development of the problem, GI bleeding. I don't think that we can discuss this issue of this continuum of NSAIDs with respect to risk without discussing the difference in risk in patients who may be given these agents. I think they go hand in hand.

DR. HARRELL: I think we are making the problem a lot simpler than it really is because when you are looking at different safety outcome in acute MI studies, there is a huge spectrum of safety events. Even when you are just looking at stroke as an adverse event from thrombolytic therapy, there is disabling stroke and there are milder strokes. You can't just count strokes. You have to look at the severity of the stroke.

Ever since I have been working for FDA, for 14 years now, I have heard the phrase risk-benefit assessment and I have still never seen one done in 14 years. And, I think we need to take some lessons from the cancer area where they actually do this, and they have ways of trading off toxicity with efficacy and quality of life, and the assessment of patient utilities now is getting very mature and we need to see some of this utility assessment and disutility assessment for adverse events used and incorporated in the tradeoff.

DR. WOFSY: It sees to me, and I may be wrong -- I don't know the origin of this question, that this question comes, at least in part, by some second thoughts based on what has happened in the course of the development of COX-2 inhibitors, and did we do it the right way; should we have done it a different way?

So, I might speak up actually for what was done. It doesn't seem to me to be necessarily wrong. In fact, this is a good example. This was rational drug development. It was based on a biological principle that was important and that addressed an important problem in clinical medicine, and it led to a specific hypothesis and that hypothesis had to do with GI toxicity. And, that is what was looked at. It would be very hard to go back and try to understand why you might have wanted to do anything differently than that. In the course of doing thorough examination of that question, other safety issues were explored and came out that turned out to be important and raised new questions for us. And, it seems to me that that is okay too, that in this particular instance there was a reason why organ-specific toxicity was the right thing to look at first and it was, of course, appropriate then -- especially since this became such a widely used agent -- to go beyond that and look broadly at other things.

It might be that for a different agent that wasn't developed specifically focused on a single organ toxicity that wouldn't be the right approach. But, in this case it seems to me it is a rational approach and it would be hard to even picture the discussion that would have led down a different pathway from the beginning.

Having said that, however, I actually think it is worth taking seriously the comments that were made in the public session this morning about the thoroughness of a safety review before approval. I don't think there was anything wrong, anything that should be second-guessed, in my own view, about the sequence of organ-specific evaluation first and overall safety toxicity later but I do think that the point that was made is very pertinent. That is, if a drug doesn't have an efficacy advantage and is being put forward primarily because of its safety advantage, a particularly thorough safety evaluation needs to happen, in whatever sequence, before a final decision is made. And, if I were to sort of think back on the lessons learned on the sequence of events with cyclooxygenase inhibitors, COX-2 inhibitors in particular, it would seem to me that that might be more the lesson than the order in which this is done.

DR. HARRIS: Thank you. In other words, if I am hearing you correctly, the sense with respect to overall safety is that there is a level of satisfaction with what has been done and it is probably difficult to do anymore.

DR. WOFSY: My goodness, I must have misspoken!

DR. HARRIS: I must have misunderstood.

DR. WOFSY: No, I certainly didn't mean to imply that there is no more to be learned here that is important regarding the safety of this agent. I was more interpreting -- maybe I have interpreted the question wrong -- about whether we should focus first on overall safety and then move to organ-specific safety or vice versa. I think it was that question more that I was addressing. So, I didn't mean to be implying that we are done.

DR. WOLFE: I want to echo what he said. Again, we are looking through a retroscope. It is always easy to do that. But, when I teach students, fellows and residents, that this is the best example we have ever seen of the bench to bedside. The discovery was made. The hypothesis was put forth and it was tested. Indeed, in all the preliminary studies it looked like the hypothesis was correct, that these drugs were GI sparing. The next was to do a real-world study, and that was done. Then, again, the prediction was, after the objective was proven -- it definitely was afterwards that there may be another issue regarding the balance between thromboxane and prostacyclin and that was examined and it came out in the trials.

So, I think everything done to date was really appropriate, as you said, but there are other studies to be done in the future and I think the advantage of some of the newer drugs coming out will be that they have seen what happened with the first drugs developed in this class.

DR. HARRIS: Let me just ask you again, so from what I am hearing with respect to organ-specific safety is that the way in which the trial was framed, with respect to overall safety you are comfortable with what was required and what was done?

DR. WOLFE: Overall safety ended up being assessed, and I think that is very important if we are looking to tell a patient or a physician is looking to tell a patient here is a drug, we can't say that globally this is going to be a much safer drug. I think we all agree with that. On the other hand, we do know patients are all different, and we know people have certain histories and certain risk factors that would mandate or suggest a different class of drug for that individual or different drug within the class.

I mean, the future is going to be more than that as well. There are drugs in every class that are metabolized differently and we are going to have profiles on cards which say which drug in which class we should be using. It will be much easier than a guessing game because these are being developed now.

DR. NISSEN: I am going to dissent here a little bit just for the moment and say that I think that there are some messages here. Let me see if I can articulate this. You know, there is lots of history of drugs that were designed well, designed for a specific purpose that had an effect on another organ system that wasn't fully anticipated. As a consequence of that, the potential does exist to make a serious mistake when you focus all the attention on the early development on this target organ and kind of concept.

So, in pre-approval I really do think we don't want to lose the FDA's focus on overall safety because, you know, again, I can imagine a drug -- let's take a worst case in this class. Let's take a case here where the GI safety was improved but where the cardiovascular safety produced, let's say, ten times as many myocardial infarctions -- that sort of thing. Now, hopefully, that would come out in general surveillance but sometimes when you do a target organ oriented drug development the population you study may be much narrower. It may not include so many patients at risk and then the study gets out in general use and you find out that there is an unforeseen toxicity involving another organ.

So, I think there are some lessons here that maybe ought to be revisited as we go forward in other areas, this one included, where we put a pretty high priority on showing the general safety issue, at least early on, concomitantly with the specific organ safety with the idea that postmarketing surveillance can pick up some of this but you would sure like to know about that before you release the drug. I would have liked to have known about the cardiovascular issue here before these drugs got out into general use, and we really didn't know that at the time.

DR. HARRIS: Can I ask a question here? I am sorry to impose. Because perhaps the cardiovascular risk rose in the course -- you know, it was after the event, can one address overall safety with the same rigor that you can organ-specific safety because overall safety is broad and there are any of a number of things in overall safety? And, if you are doing a safety study, the question is you have an organ and you can be quite rigorous about that, but overall safety, can you address it with the same rigor?

DR. NISSEN: You can't. So, if you know enough about the drug you might be able to have some candidate organs to look at. If you look back, there were some folks that predicted this. I mean, Fitzgerald told us pretty early on, he said, gee, there is this balance between prostacyclin and thromboxane; I am worried here that you are going to change that balance unfavorably. And, I think we have to be really listening to folks like that. No, you can't do every organ system with the same rigor you do the target organ system, but maybe if there is a little bit of anticipation maybe you can do some things early on that will give you the signals you need to know whether or not there is more risk there than you know about.

I mean, obviously, the retroscope is a wonderful instrument here and we all have that advantage, but if you go back and read what Fitzgerald wrote, he anticipated this potential problem.

DR. CALLAHAN: To answer your second question, I think it is difficult to do every organ system but, like Dr. Nissen pointed out, if there is evidence for certain body parts or candidate areas to at least study those. The message I get over and over from today's message is we are treating a whole patient, not just the muscoskeletal system or the GI, and the overall toxicity is important in the bottom line because it is the entire patient that these drugs are treating, not just the one system.

DR. HARRIS: Let me again come in here. I think the issue is not so much that one shouldn't monitor overall safety. Should it be similarly monitored? I don't know if I am over-interpreting what the FDA meant, but that is my interpretation.

DR. GOLDKIND: The spirit of the question, in a sense, is to give us guidance for future drugs that may be in development, obviously most specifically COX-2 selective agents, although conceptually it could extend to any drug group where a product is developed with a safety advantage in mind. And, there are minimum requirements for exposure before drug approval but those requirements generally will not pick up rare toxicities, nor will they give you robust comparisons to any other drugs or placebo for even events that are not that rare so that making a safety comparison is difficult from the minimum database that is required for approval of a drug. The question is aimed at soliciting your thoughts on whether this is a good approach and, again, preapproval versus postapproval for drug development where a specific organ safety claim would be considered because this would be a marked change from the past in terms of what we would ask for preapproval, to have a large safety database like this, particularly a comparative safety database.

DR. HARRIS: Thank you. I will take two more comments.

DR. PINA: I think there are several levels here that need to be examined. There is the level of possible toxicities which the sponsor may know from their studies in-house with the very early studies, and some of them may be in vitro studies and some of them may be in animal studies, that some toxicities may be expected.

I think you also have to look at the patient population that it is going to be applied in, and if you know the rates of certain concomitant co-morbidities and diseases in that population it will help you focus on those specific toxicities. In this group and yesterday as well, for example, we are dealing with older patients where the risk of cardiovascular disease is very high on the agenda, particularly in the postmenopausal women, as we said yesterday, the number one cause of mortality in the United States. So, you are already focusing on a group that is targeted to have a certain rate of accumulation of events in a certain organ system. You could say the same for malignancy.

What I think hasn't been discussed here, and I kind of hinted at it yesterday, is that the majority of these patients are on multiple drugs and I didn't see anything today about drug-drug interactions, and I think that is critical. And, in our cardiovascular arena, as Steve has put well, we have had drugs that have been released because of a very specific study that proved improvement. I can name at least one in the heart failure arena, and when it got out into public use very quickly the FDA saw all the interactions with all the drugs that these patients were on, for example, the statins. A lot of these patients are also on statins. They are on aspirin; they are on statins; they are on blood pressure medicines and I think that is critical because the applicability of these data to patients who are on multiple drugs -- we can't say. I don't know it; it is not there.

DR. WOLFE: We are all saying the same thing but in slightly different ways. None of us wants to put a drug out there that has serious toxicity. The question is when do you pick it up. Let's consider here a very specific instance. Fitzgerald's lab article came out in January, 1999; celecoxib was approved a month earlier. You know, it was already approved. That wasn't foreseen and also may not have been picked up in studies leading to approval because maybe aspirin was used in those studies and would have masked that effect. Not only that but if it was a big, big, you know, 20-fold increase it may have been picked up. That is why you do have postmarketing surveillance. You have Phase IV studies to pick up these possible toxicities and the cardiovascular example is not exclusive. I mean, we just had two drugs in GI this year -- excuse me, in 2000 taken off the market because toxicity was picked up that wasn't seen initially when the drug was approved. That is why we monitor drugs after they are approved as well.

MS. MCBRAIR: I think because of the increase in the ability of the drug companies to market these drugs the overall safety is important and needs to be done earlier than perhaps used to be the case. There are a lot patients now coming to doctors' offices with already preconceived ideas of what they would like to be on; what they think they should be on and that didn't used to be the case. So, the overall safety seems to be a really important issue.

DR. HARRIS: Thank you. If there is anybody in the audience -- and no more than two -- if there is anything additional, anything that was not said earlier with respect to this question that one feels might provide some more information, then let me invite it. If not, I would like to move on.

[No response]

Do you think you have gotten enough guidance here?

Let's go to the last question, both the VIGOR and the CLASS studies, as well as postmarketing data, confirm the higher risk for complicated ulcers in elderly patients and in patients with a prior history of ulcer disease. This increased relative risk was seen across all comparators. Current labeling notes these as a risk factor. Given that COX-2 selective agents may be regarded by some as having a better GI safety profile, does current labeling provide adequate awareness for prescribers regarding the increased risk in these populations? Dr. Nissen?

DR. NISSEN: I was very troubled by this question and I am going to tell you why I was so troubled by it. Those very same factors increase the risk of cardiovascular morbidity and mortality. So, I don't know what to do because the elderly are the ones that are most likely to have unstable angina, acute MI or sudden cardiac death. So, it is a mixed bag and I don't know whether the net benefit here exceeds the net harm. You know, it actually would be a lot easier for me to advocate a COX-2 inhibitor for a young patient without cardiovascular risk because I can see where the benefits would be outweighing the risks. But when you consider that an atherosclerotic event is the cause of death in about 50 percent of the American population, you are talking about the potential for an awful lot of morbidity and mortality as you treat those patients with agents that may increase the risk of that endpoint. So, I think because of the mixed data on GI safety and cardiovascular safety, it is hard to make that recommendation.

DR. HARRIS: Dr. Nissen, do you get a sense that that safety that we saw today was carried over? It was equally safe in your mind with respect to patients who were elderly and had a history of ulcer disease?

DR. NISSEN: I am sorry, I don't understand exactly what you are asking.

DR. HARRIS: In other words, as far as COX-2 inhibitors used in these particular patient populations with increased risks, the elderly and those who have had a history of ulcer disease, do you have a sense here that the COX-2 inhibitors were without risk? In other words, should there be a labeling change?

DR. NISSEN: Well, they were certainly favorable with comparison to the naproxen comparator. So, in that sense, given the fact that if you have, let's say, a seven percent chance of having a bleeding ulcer and you can reduce that risk in half the absolute benefit to those patients is relatively large in terms of the number of patients you actually benefit. So, I did see some evidence of at least proportionality in benefit among the elderly, if not greater than proportionality.

DR. WILLIAMS: When I look at this question I would say we all recognize that age is a risk factor for many things besides just GI bleeding, however, the benefit, as was just stated, of GI protection was extended to the elderly. They were safer on a GI protective agent. However, I would give the caveat, yes, but a healthy elderly patient who has a risk for GI bleeding is going to be benefited by a GI protective agent, however, if they have a need for cardioprotection and they have to take daily aspirin, like the elderly and the young, if they are on aspirin I think you use the benefit of the GI protection from a COX-2 specific drug. So, I think what needs to be addressed is not the fact that the elderly are a risk factor but, as we have already addressed earlier, aspirin and COX-2 agents together take away some of the benefit of the COX-2 agent.

DR. HARRIS: Could I interpose again? Is the current labeling adequate?

DR. WILLIAMS: Yes, provided they accept what we have said about aspirin earlier.

DR. HARRELL: This is one place where I think statisticians have something unique to offer, and I would like to say that in all the clinical trials that are done the proportion of trials in which all the information that could be obtained from the trial is obtained from the trial is very low. There are so many opportunities for doing modeling on good data, it is amazing. And, one of the models that is needed is a model of who gets certain adverse events but also who gets certain benefits.

There is one example in the literature which I would like to see replicated in this area. It is tooting my own horn maybe too much but in the GUSTO I study -- these are acute MI studies where you have these huge numbers of patients so it is easier to do. That study had 40,000 patients in it, but we had a risk model developed from the clinical database, and published a paper that shows, in a fairly easy to use scoring system, how you can estimate absolute clinical benefit for an individual patient. You could also, which we didn't do but you could also make that net benefit after you subtract out hemorrhagic strokes and certain adverse events. But if you look at that paper and see the scoring system, to me, it is something that could almost be in labeling some day. It is not that hard for a physician to carry out and it is something that you could make even easier with a computer program. But it is just a table to go through and you add up certain points and, you know, the bigger MI is or the older you are, or the more anterior the infarct was, or whatever, you get more net clinical benefit from TPA or streptokinase, and I would encourage people to look at that.

DR. CRYER: With respect to the question that you have asked, I think that there are three messages that need to be relayed. One, which is one that we have overlooked to a certain extent in our discussion, is that there is an intrinsic risk to certain risk factors. GI bleeding in and of itself, older age in and of itself in the absence of NSAID exposure carry an intrinsic risk.

The second message that I think needs to be transmitted is that in these patients it appears that they certainly would benefit from a COX-2 specific inhibitor from the perspective of risk reduction.

But, along those lines, the third message is that the risk persists. So, there appears to be an intrinsic risk. They will benefit but even in those who benefit there is a persistent risk for complications.

DR. HARRIS: Can I ask, when one says about risk here, does one say risk compared to the use of another non-steroidal anti-inflammatory drug? In other words, if you were to use a COX-2 it would be better than using perhaps another COX-2 non-selective drug.

DR. CRYER: Well, I think those data were clearly shown in the studies that we have seen. If you look at the high risk populations from, let's say, the VIGOR trial, their relative risk was clearly reduced in comparison to naproxen. Did I answer your question?

DR. HARRIS: Yes, part of it. Is it reduced to the intrinsic level? In other words, would you say that there is no added risk?

DR. CRYER: I can't say that with any certainty.

DR. HARRIS: Okay. I think the labeling actually, as it is right now, reflects the fact that there may be added risk.

DR. CRYER: It does.

DR. WOLFE: But you have asked a question about the elderly, and looking at the general warning, I don't think there is anything about the elderly in there. Is it in there? Is it in there about bleeding specifically? It is in the hematologic and you want to add that the risk is across the board. It is proportionally diminished, at least in the VIGOR study by age, but there is still a risk. If you look at an 80-year old on Vioxx, it is greater than a 20-year old on peroxicam.

DR. CRYER: If I may, Dr. Harris, for the purposes of this discussion, I have underlined what the labeling says with respect to this issue: NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and, therefore, special care should be taken in treating this population.

DR. HARRIS: I get a sense here that most of us feel this is adequate as it is, and perhaps there isn't a need to do any more. If anybody objects, could they raise their hand? I will take the absence of raising of hands as the guidance you have gotten.

Are there any other burning issues to be raised? If not, we come to the summary part of the proceeding.

DR. DELAP: Do you view the business as concluded then? Is that what you are saying?

DR. HARRIS: To my knowledge, yes.

DR. DELAP: I would like to say thank you very much for all your hard work over the last couple of days. It has been a very enriching experience for us in terms of all the comments and recommendations we have received, and we thank you very much for your comments. That goes for the sponsors as well. I think both the sponsors did a tremendous job of preparing very massive databases in a very thoughtful fashion.

DR. HARRIS: Thank you. Closed.

[Whereupon, at 4:10 p.m., the proceedings were adjourned]

CERTIFICATE

I, **ALICE TOIGO**, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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